THE PRACTICE OF MEDICINE

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BY

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FIFTH EDITION

WITH 518 ILLUSTRATIONS INCLUDING 50 IN COLOUR

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TO

MY WIFE

SARA CALDWELL MEAKINS

THIS BOOK IS

AFFECTIONATELY DEDICATED

PREFACE TO FIFTH EDITION

The task of writing a new edition of *The Practice of Medicine* is becoming increasingly difficult. This is so for a number of reasons, of which the most specific is the upsurge of specialized technics. In other words, the wide view of medicine is being clouded by a multiplicity of minutiae which are beyond the technical capacity or facilities of the general physician. Indeed, the requirements of medical practice are becoming so complicated that there must be, in the near future if not immediately, some organized effort to bring these diagnostic and therapeutic facilities to the doctor and the patient. This general absence, however, does not afford an excuse for neglecting to include or even emphasize them in the present text. The fortunate patients who have access to metropolitan clinics have these facilities readily available. However, they make up a comparatively small percentage of those who suffer from ill health. Furthermore, human disabilities do not in the main come from rare or exotic diseases, but are due to more obvious and too often neglected causes, such as economic, social and emotional situations.

If one reviews the progress of medicine over the past three generations, it becomes increasingly apparent that a logical but not always necessarily a connected developmental progression has occurred. The great school of pathological anatomy led by Virchow pointed the way to *a basic concept of disease*. The almost coincident concept of microscopic agents causing many of these anatomical changes was placed on a firm foundation by Pasteur, Lister and Koch. The progress of bacteriology found gaps in the explanation of many infectious diseases, and so in time the *role of rickettsiae*, viruses, protozoa and other agents was authenticated. Medicine now had a concrete problem to solve, namely, the search for specific methods of protection against or antagonists to these agents. So were born the modern methods *of protective inoculation and chemotherapy*. But medical thought in the meantime had also been concentrated upon disturbances of function, or what today we are inclined to call pathologic or abnormal physiology. It was a belated but obvious progression from the school of pathological anatomy. *In other words*, the experimental method was again introduced. On this was developed the concept of physiological deficiencies and excesses and other perversions of function. It was but a short step to link these with anatomical abnormalities. But this was not always successful and so there still remain gaps in our complete knowledge. For example, why diabetes mellitus? *It is held to be due to* a primary defect of the islands of Langerhans. But the evidence is not always, one might even say it is seldom, conclusive.

It was a natural progression in physiology that biochemical and biophysical technics should steadily become important and even fundamental frontiers in the elucidation of abnormal processes. So now the biochemist, sterol chemist, colloid chemist, enzymologist, biophysicist (including experts in atomic energy research), parasitologist, protozoologist, epidemiologist, mathe-

matician and many other specialists dealing with man as an organic animal are focusing their spotlights on his physical defects This is as it should be but sometimes enthusiastic hypothesis based upon a modicum of fact has far outstripped reason This has not been kept within rational practice by the many uncontrolled publications in the professional as well as the lay press

During many of these decades man was mostly concerned with man as a biological specimen rather than as a loving hating propagating thinking complete unit In fact most physicians relegated the emotional difficulties to their "nerves" or some other equally disparaging term It must be conceded that the older physician was an unconscious psychologist but for a long period the advances of medicine did not leave room for any concept which could not be measured by a formula or in milligrams This is not intended as an indictment but simply a fact in the progress of medical thought The blame for this point of view might with justice be laid at the door of the psychiatrists There was not much difference between the mental outlook of the therapeutic nihilist of 1900 and that of the average psychiatrist of 1925 There were however as always a few far seeing men who could not accept this fatalism These were not confined within the discipline of psychiatry but within their numbers there were psychologists sociologists economists educationalists anthropologists philosophers statesmen labor leaders industrialists and others The dignity of man in his social economic and emotional environment was their concern They did not deny that a physically healthy body was a just and reasonable requirement but this was of little avail if the spirit and mind were in travail So there gradually evolved a more realistic concept of disease as a whole Psychiatry took to itself a more comprehensive place in medicine The interactions of psychology physiology biochemistry endocrinology and even ultimate effects upon anatomical structure are now being appreciated and are taking their places in the understanding of all health

In the present edition it has seemed advisable to remove the sparse section on psychiatry and to replace it with one on psychosomatic medicine There is a large body of opinion which takes exception to this term but it must remain until someone has the ingenuity which this writer has not to coin a better one This task has been undertaken by Dr Frederick R Hanson to whom I express my sincere thanks

The chapter on the nervous system has been maintained for several reasons As a classical description of neurological lesions it has few if any equals for a text of this character It was the creation of a great neurologist Dr J N Petersen whose death at an early age was a great loss to the medical science and to a host of devoted friends among whom this author was proud to be numbered

The rapid advance in chemotherapy and antibiotics has in a way simplified the treatment of infections but it has also somewhat complicated the description thereof In order to reduce reduplication a chapter has been devoted to this subject In this has been condensed the principles of chemotherapy and antibiotics and the indications and manner of their use It is hoped that by this

means a clearer understanding may be obtained upon which further advances may rest. New discoveries are almost monthly events but the fundamental principles remain unchanged.

In all the chapters a valiant attempt has been made to bring them up to date but with the tempo of the times this is a difficult task. Seeming sins of omission have occurred on purpose as it was felt that their validity was not sufficiently proved to warrant their inclusion. For this we make no apologies.

The chapter on the ductless glands has been largely rewritten. An attempt has been made to clarify the classical description of some of the diseases of these organs in order that it may be appreciated that there are quantitative and qualitative variations in their functions and that their interrelationships cannot be ignored or neglected.

In conclusion I wish to renew my thanks to my colleagues Dr F H Mason and Dr Walter deM Scriver for their continued assistance and cooperation. Also I would desire to thank Dr Martin Hoffman for many helpful suggestions and timely criticisms.

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PREFACE TO THE FIRST EDITION

It would seem audacious for one to attempt to write a treatise on the practice of medicine at this time when specialization has become so highly developed. This volume is not intended for the specialist, nor does it aspire to be encyclopedic, but rather for the student and practitioner, to assist them in solving the numerous puzzles and problems with which they are daily confronted. So far as the patient is concerned, disease consists of symptoms. It is for these that he or she consults a physician. They represent the earliest manifestations of disease and therefore are of primary importance. They are the clues to the clinical riddles. For this reason they have been given particular prominence and where possible their causation has been described and their significance has been pointed out.

This is a pictorial age and many factual data are capable of graphic records. Therefore I have diverted from the usual custom in textbooks on the practice of medicine and have inserted many illustrations with the hope that these may be more informative than a word description. I have kept before my mind the fact that the patient presents symptoms and signs which indicate disturbances of function and from these the pathological conditions may be traced and identified. It has been my hope that this book would be a guide to the practice of medicine as well as a description of individual diseases.

I am particularly indebted to my colleagues for their contributions, Dr E H Mason for the chapters on Diseases of Metabolism and Diseases of the Ductless Glands, Dr Walter deM Scriver for the chapter on Diseases of the Urinary System and Dr J Norman Petersen for the chapter on Diseases of the Nervous System. I also wish to express my thanks to Dr J S L Browne and Dr David L Thomson for help and advice especially in matters of the ductless glands. To both authors and publishers who have so generously assisted by permitting the use of their published illustrations I wish to express my sincere thanks. Figs 456 483-487 490 492 are reproduced from the Army Medical Bulletin No 1 January 1913 Photomicrographs of Spirochetae Entamebae, Plasmodia Trypanosomes Leishmania Negri Bodies and Parasitic Helminths by permission of The Surgeon General of the United States. To my secretaries Miss M R Imrie and Miss V L Davidson I am indebted for their care and patience in preparation of the manuscript, and to my librarian Miss Genevieve Dunne for the verification of the references.

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THE PRACTICE OF MEDICINE

CHAPTER I

AN INTRODUCTION TO THE PRACTICE OF MEDICINE

The practice of medicine is probably the most entrancing profession in the world. As it deals with human beings it requires a complete understanding of, and sympathy with, all aspects of human life. One, to practice it wholeheartedly, must be a combination of a confessor, a judge, a counselor and, above all, a friend. The time of the "family doctor" is held by some to have passed away. It would be unfortunate if such were the case. The physician who "knew the case" from birth had a perspective to which no one else might possibly attain. The spirit of specialization and mass production has invaded the medical profession. It has probably improved and stimulated the technic and zeal of the average medical practitioner. It has undoubtedly elevated the average health of the citizens at large, but has it done so without the loss of a certain *finesse* and understanding of the human frailties and the helpful counsels of an old and trusted friend which made a profession instead of a trade of medicine? I believe that many of the rising generation of medical practitioners are returning to this humanistic relationship.

The complete understanding of the patient who seeks help is the first requisite for successful treatment. An individual seldom consults a physician unless there be something which interferes with his well being either in regard to his work or his pleasure. Thus it is so much easier to comprehend his discomfiture if one has an idea of his social and industrial environment. If one has not, it is incumbent that as far as possible this should be ascertained and so from this point may a start be made. This is the present concept of the industrialist and the industrial physician.

But, in acute diseases an early diagnosis is essential. Thus it is important to have a thorough conception of the early manifestations of the acute diseases or, in other words, an understanding of the causation of symptoms and their importance in relation to the time interval of their occurrence. Many symptoms and signs have an entirely different significance depending upon whether their onset be acute or explosive on the one hand, or insidious or intermittent on the other. A sudden disturbance of the normal processes of the animal organism gives rise to much more violent consequences than does a gradual dislocation. The reason for this is to be found in that uncanny faculty of the animal organism which, if given a sufficient period of time, can marshal to its aid many compensatory means to accommodate itself to the new environment. In order, therefore, to recognize the processes which are being initiated it is of importance that the earliest manifestations of disease processes should

be recognized and interpreted in their proper perspective and laid to the door of a definite etiological cause which is present in all diseases if we had sufficient knowledge to recognize it

There are several ways to view diseases depending upon whether one is most interested in the living or the dead All diseases when taken as a whole run through a reasonably definite "life cycle," although this statement must be modified to the extent that one cannot expect every instance of the same disease to run on a time schedule as to the appearance of each phase, or that each phase will be equally prominent and distinctive in each case The fallacy of considering all diseases from the "morbid anatomical" viewpoint is that this is usually a final stage and does not sufficiently illumine the conditions of disturbed anatomy and physiology that have gone before It is true that a great deal may be inferred from the final dissection but this in many instances does not give the clue to the variegated and important disabilities which have been present during life Furthermore, there are numerous disturbing functional derangements which cannot be explained on any known anatomical basis In fact death frequently occurs and no adequate anatomical explanation can be found It, therefore, behooves all physicians, no matter what their therapeutic inclination may be to view the human organism as a going concern, subject to various functional defects or disorders, the causes of which should be understood during life The anatomical changes found after death are of significance only if they can shed light on the cause and progress of the functional failure of the living organism

One of the great handicaps to the practice of medicine is the isolated viewpoint obtained of the various phases of the majority of chronic diseases The acute diseases are usually viewed in their entirety by one physician, that is during the full period of their relatively short course But then there is the residue or sequela which may not be manifested for years to come The complete physician should have this opportunity but unfortunately the medical practice of the day has tended to divide into compartments These may be only sufficiently large as to include diseases of one organ or system even individual diseases or even at times isolated symptoms The broad panorama of disease may thus become obscured As already mentioned diseases run through a life history which follows an immutable course barring accidents the question of time and age and rate of progress By this is meant that chronic diseases may develop in their natural course either slowly or rapidly depending upon individual characteristics If it be rapidly then the whole life history may be run within a short span and the chances of other disasters interrupting its course by premature exit are less likely On the contrary the progress may be so slow as to be almost imperceptible Then the chances of some other accident interfering with the full development of the disease are more likely

One of the disadvantages of studying or viewing disease from the purely anatomical standpoint is the tendency to explain all disabilities solely on an anatomical basis This is wrong except so far as when it be possible to interpret functional deficiencies as resting upon such a basis A man without one

leg is obviously handicapped So also is an organ without an adequate blood supply But it is essential that we be able to determine the anatomical defect without seeing it Therefore we must be able to reason from functional derangements that such and such anatomically progressive lesions are in the process of development Many instances of this comprehensive functional anatomical method of deduction will be illustrated in the following pages

When a patient seeks medical advice he brings a history of what has gone before with a definite time relationship indicating progress He presents a certain physiological or anatomical disturbance, the magnitude of which from the point of view of the functional disturbance at the moment indicates the present stage of progress of the disease Many of these disturbances may be of temporary significance due to unusual strain or indiscretion which by correction may recast the actual condition into its proper perspective So a hasty judgment as to the future is inadvisable Furthermore, a comparatively mild or unimportant malady may be exaggerated in its manifestations by an overanxious or distressed spiritual outlook or desire to entice sympathy and attention All such factors must be carefully weighed and assessed by the discerning physician He must view the whole progress of the disease with sympathetic understanding and keen insight into its character and that of its host

A mere diagnosis as to the probable and fairly obvious status of the moment is not sufficient He must be patient and capable enough to assay the present real situation and at the same time to clear the clouds of apprehension and fear, to be truthful in the presence of impending catastrophe when necessary but tempering the decision with mercy as a brave and fearless spirit oftentimes surmounts what seem impossible obstacles continuing onward in usefulness and with joy to others It therefore behooves all physicians to beware of the absolutely hopeless prognosis with the inclination to hold out a gloomy future futility and dependence or condemn to a short period of life This should be avoided for two reasons in the first place we do not always know whereof we speak and second such a statement in any case can do no good and is apt to discourage utterly one who otherwise might finish out his life in comparative cheerfulness and pleasure It is not death that is so fearsome but the contemplation of the march toward it when the journey is known to be short The spirit is filled with terror lest it fail

THE APPROACH TO THE PATIENT

An individual seeks advice of a physician either because something interferes with self preservation self propagation or self comfort Other things do not matter from a physical point of view It is true they may be economic or spiritual and as such are camouflaged under a more indefinite physical disguise But, in spite of these clouds of darkness they must be disentangled

Probably there is no more important approach to the elucidation of "disease" than a careful history It is often neglected as being of little moment as compared to the "physical findings" or the "laboratory findings" which are presumed by many to be of greater importance This at times is true

by pericardial effusion and scarring respectively Soon after this Lower s fellow countryman Mayow in 1674 published his *Tractatus Quinque* in which the oxygenation of the blood in the lungs is clearly presented, Mayow s fifth treatise was one of the very earliest on rachitis *

Mention should be made next of two other important medical writers of the last half of the seventeenth century who although not dealing specifically with heart disease contributed significantly to the subject Kerckring in Amsterdam in 1670 wrote a treatise on pathology called *Spicilegium Anatomicum* in which with apologies to his teachers and colleagues he pointed out their grave error in considering as evidence of heart disease the postmortem clots found in the heart by this one brief statement he altered radically the current misconception about the heart wiping out doubtless fully one half of all so-called heart disease The other writer who did so much at that time to elucidate somewhat the still very dark subject of heart disease was Bonetus who in two editions of his *Sepulchretum* (1679 and 1700) presented among more than two thousand other case reports with clinical notes and autopsy findings several hundred whose symptoms and signs were to be ascribed to lesions of the heart and great vessels These cases he collected from all possible sources they make an invaluable compilation which served as a basis for his successors including Morgagni one hundred years later (*De Sedibus et Causis Morborum* 1761) In this rich clinicopathologic collection there were many firsts involving all parts of the body There were the earliest associations of dyspnea with cardiac enlargement sudden death with calcareous aortic stenosis and collapse and early exitus with a high degree of coronary artery narrowing

Early in the eighteenth century two important books on the heart and some of its diseases were published in France and Italy respectively by leading authorities of their day The first entitled *Traité Nouveau du Coeur* appeared in 1715 prepared by Vieussens who in his youth thirty years before had published a pioneer work on the nervous system called *Neurographia* An excellent description of the mechanical effect of severe mitral stenosis on the lungs with resultant congestion and dyspnea appears in this work by Vieussens The other writer was Lancisi physician to Pope Clement XI to whom he dedicated the volume entitled *De Motu Cordis et Aneurysmatibus* which was published posthumously in 1728 Lancisi described engorgement of the neck veins associated with dilatation of the right ventricle and discussed cardiac enlargement at some length An illustration of the very rich nerve supply of the heart is included in this volume and was bettered only years later when in 1772 Neubauer published a drawing of a beautiful dissection of the sympathetic innervation of the heart Lancisi was an able and prolific writer and had earlier published several books on medicine and other subjects such as fungi One of these medical books is unique in that it was entitled *De Subi*

* Since writing this I have within the last few months acquired a still earlier work by Mayow a fascinating booklet published in 1671 and entitled *Tractatus Duo Quorum prior agit de Respiratione Alter de Rachitide* The first printing of this little book appeared in 1668

taneis Mortibus (On Sudden Death) (1707) it contained autopsy reports of individuals who had died suddenly and whose postmortem examinations had been carried out at the express request of the Pope an instance long forgotten of the liberal enlightened and scientific attitude of the Church

Now we come at last to what is often called the first textbook on heart disease itself namely the *Traite du Coeur* by Senac published in Paris in 1749 It has much more of clinical and practical importance than had been presented by any earlier publications This is particularly true of treatment of which there was scarcely any before two hundred years ago Senac mentions the value of bleeding and sedation in heart failure and of quinine in rebellious palpitation a very early forerunner of the relatively recent application of quinidine to the treatment of cardiac arrhythmia Following Senac various textbooks on heart disease have appeared in different languages most of them however after a delay of a half century or more Included among them are in French those of Corvisart Napoleon s physician (1806) Huchard (1889) Vaquez (1921) and Laubry the present leader of the French school (1930) in German those of Kreysig (1815) Traube (1856) Fraentzel (1889) Romberg (1906) Edens (1931) and Hochrein (1941) in English those of Hope (1832) Stokes (1854) Flint (1859) Steell (1906) Mackenzie (1908 4th edition 1925) Hirschfelder (1910) White (1931 the present edition the 4th 1951) and Levine (1936 4th edition 1951) in Italian those of Testa (1810) and Luisada (1938) and in Spanish that of Cossio (1935 4th edition 1949)

More important as a rule than these textbooks however have been mono graphs on important new technics or on etiologic diagnostic or therapeutic discoveries beginning with Auenbrugger s introduction of percussion in 1761 in a little book in Latin entitled *Inventum Novum ex Percussione Thoracis Humani* but not well known until Corvisart s translation in 1808 Percussion was further developed by Piorry (1828) and Skoda (1839) This was the first of the technics which have been slowly but steadily introduced into the practice of medicine to improve the diagnosis of heart disease One of Cor visart s pupils was Laennec whose introduction in 1819 of the stethoscope for mediate auscultation of the heart and lungs was a very significant advance *(De l Auscultation Mediate)* A century later Cabot and others began to try by electrical methods to broadcast by separate earphones or loud speaker to groups and classes the heart sounds and murmurs of an individual patient and to record them on phonographic records while simultaneously Lewis and others began to photograph on moving film by way of microphone and galvanometer the auscultatory findings with simultaneous electrocardiogram (phonocardiography) These technics slowly evolved to their present higher degree of usefulness with the help of Einthoven and Geluk of Geckeler of Mannheimer and of Sprague and Rappaport

One hundred years ago (1846) Hutchinson introduced the determination of the vital capacity of the lungs Another interval elapsed before the fourth helpful technic in the study of the circulation came to pass this was the

sphygmograph which first developed by Marey in 1860 gradually evolved into a practical instrument the ink polygraph in the hands of Mackenzie who printed many of his graphic records in his classic on *The Pulse* in 1902 and who with the help of Wenckebach called attention to the serious significance of pulsus alternans The next important technic namely the sphygmomanometer was slowly introduced by a group of workers (von Basch 1881 Potain 1889 and Riva Rocci 1891) another decade or two passed before blood pressure measurement became a routine clinical procedure nearly two hundred years after the English parson Stephen Hales had accurately measured the arterial pressure of a mare in 1733

Roentgen late in 1895 announced the discovery of his x rays and the following spring Williams of Boston published an x ray picture of the heart In this field there has been a steady advance ever since with the introduction of orthodiagraphy of the heart by Moritz in 1902 of teleroentgenography by Kohler in 1905 of roentgenkymography by Stumpff in 1931 (suggested by Sabat in 1913) with further development recently (1945) by Chamberlain Henny and Boone by application of photoelectric cell and galvanometric graphic recording of angiocardiography by contrast injections by Forssmann in 1931 Castellanos in 1937 and by Robb and Steinberg in 1938 and of roentgencinematography by Reynolds in 1934

Another technic of the greatest value has been electrocardiography The study of the electrical activity of the heart introduced nearly a hundred years ago by Kolliker and Muller (1855) was carried on laboriously in the physiologic laboratories for nearly fifty years before a practical instrument (the string galvanometer) was developed by Einthoven in 1903 to replace the clumsy capillary electrometer which had been employed by Waller in 1887 to take the first human electrocardiogram Nearly another ten years passed before clinical electrocardiography began under the stimulus of Kraus and Nicolai in Berlin and of Lewis in London In the last twenty five years there has been a considerable amplification of the use of the electrocardiograph in the diagnosis of heart muscle injury and especially by the application of unipolar leads to the chest wall itself

Finally with regard to special diagnostic technics one should mention cardiac catheterization which first introduced by Forssmann who experimented on himself in 1929 has now evolved through the help of Cournand Dexter McMichael Lenegre and their colleagues into a routine practical method of intracardiac and pulmonary artery blood gas and blood pressure measurements to aid in the more accurate diagnosis of congenital and other obscure cardiac defects

Leaving the history of the introduction of the diagnostic technics which began with Auenbrugger s discovery of the value of percussion in 1761 let us proceed with other historic advances in our knowledge about heart disease and first about symptoms In 1768 Heberden described angina pectoris and gave it its name although he did not connect it with the heart he knew that it was a dangerous symptom and that it was particularly likely to attack

middle aged males its connection with coronary artery disease was discovered by Jenner about 1772 but not published by him until 1799 in a letter to Parry which appeared in the latter s book entitled *Syncope Anginosa* Over one hundred years went by for some obscure reason before the common coronary complication of acute thrombosis with myocardial infarction received adequate recognition as a clinical entity by Herrick in 1912 and still another decade passed before Herrick s notable contribution became widely known Finally we owe much to Anitschkow for his demonstration of atherosclerosis in 1912 to Leary for his painstaking delineation of the lesions of coronary atherosclerosis (1935) and to Schlesinger and Blumgart for their valuable exposition of the evolution of the lifesaving coronary collateral circulation (1937–1941)

Although dyspnea had been associated for the first time with heart disease by Bonetus in 1679 having been considered a symptom solely of pulmonary or pleural disease before that time it was not until Vieussens described the mechanism of dyspnea in mitral stenosis in 1715 and Hope that of breathlessness in myocardial failure a century later (1832) that the pathogenesis began to be understood Senac and Hope in their noted textbooks in 1749 and 1832 called attention to the fact that asthma may be a complication of a failing heart with pulmonary vascular congestion Only in recent years as a matter of fact has there been a renewed interest in this relationship Still another type of disturbed breathing consisting of periodic apnea and dyspnea and associated with cardiovascular disease was described by Cheyne in 1818 and Stokes in 1854 *

Other symptoms than angina pectoris dyspnea and palpitation that can be credited to the heart are few but there is one that has been well described namely syncope due to heart block and attended by a very slow pulse this goes by the three names of its chief observers Morgagni (1761) Adams (1827) Stokes (1854) syndrome

Many signs have been named after physicians but frequently not by any means after those who discovered them first or even described them best Thus there is frequently an erroneous significance to such a designation where priority has been wrongly assigned Where possible not only for this reason but for others too especially that of preference for a descriptive term over a proper name it is more reasonable to drop the eponym and in the future not to add such to medical literature Examples of both the reasons noted above are water hammer instead of Corrigan pulse and chronic constrictive pericarditis instead of Pick s disease the water hammer pulse had been well known and described long before Corrigan and Chevers had well described chronic constrictive pericarditis fifty years before Pick There are exceptions however in which the descriptive term is so long and complicated

* My attention has been called by Dr Arlie V Bock to the fact that Hippocrates probably referred to Cheyne Stokes respiration in describing the case of a man who died of a fever in an extremely delirious state This patient had unusual breathing It was referred to as follows The breathing throughout as though he were recollecting to do it was rare and large (Hippocrates Loeb Classical Library G P Putnam New York 1923 Vol 1 p 187)

or the eponym so firmly established that the observer's name may wisely be retained

As to abnormalities of pulse form and rhythm descriptions were quite completely presented by Galen in the second century A D and by his followers for the next 1 500 years but it took many centuries before the explanation for the abnormalities was given The water hammer pulse was attributed to free aortic regurgitation not only by Corrigan in 1832 but also by his predecessors and contemporaries The first to ascribe the plateau or more importantly the anacrotic pulse to aortic stenosis is not clearly known as yet The paradoxical pulse was described by Kussmaul in 1873 and attributed when marked quite rightly to pericardial disease Extrasystoles were known to the ancients but the first reassurance about them was given by Williams in 1835 and confirmed by Mackenzie in 1902 In 1887 Bristowe described paroxysmal tachycardia as a particular entity corroborated the next year by Bouveret after whom it has sometimes been called Auricular fibrillation was identified as a clinical condition independently by Rothberger and Winterberg and by Lewis in 1909 while auricular flutter was accurately described and named by Ritchie in 1911

After the introduction of auscultation by Laennec abnormalities of the heart sounds and heart and blood vessel murmurs began to be described and explained C J B Williams described and explained the mitral diastolic murmur in 1835 the aortic diastolic murmur and both aortic and mitral systolic murmurs had been widely recognized before this in fact by Laennec himself In 1862 Austin Flint described his famous murmur of relative mitral stenosis without mitral cusp deformity In 1879 Roger reported the finding of his loud (grade 4 to 5) systolic murmur with palpable thrill just to the left of the sternum maximal in the third and fourth intercostal spaces in cases of congenital ventricular septal defect sometimes called Roger's disease The continuous murmur of a patent ductus arteriosus was described and explained by Fagge in 1873 In 1881 Graham Steell described the pulmonary diastolic murmur of high pressure in the pulmonary artery due to mitral stenosis as a rule and named for Steell Duroziez name is attached to the to and fro murmur heard over a large artery during pressure by a stethoscope in cases of free aortic regurgitation (1861) Gallop rhythm and its clinical importance were pointed out by Potain in 1875

Signs of heart failure have been recognized for many years and it was evident when the very first large collection of autopsies was made by Bonetus in 1679 that cardiac enlargement both hypertrophy and dilatation were important findings sometimes attended by dyspnea and indicative of strain although often unidentified as to type Lancisi described in 1728 fullness and pulsation of the neck veins associated with right atrial and ventricular dilatation but many years in fact nearly two centuries went by before Mackenzie spread widely abroad this important sign of heart failure When mediate auscultation came into common use a hundred years ago rales in the lungs especially at the bases became recognized as an evidence of pulmonary edema

due frequently to heart failure but this sign has often been misjudged since so many other causes may be responsible Dropsy that is dependent edema and liver enlargement were described by Bonetus in 1679 and recognized early as signs of heart disease and failure as well as being due to other diseases Munro published a treatise on dropsy in 1755

Pericarditis was one of the very first cardiovascular abnormalities noted and described as seen in Benivenio s collection of autopsies in 1507 doubtless it was known to the ancients even though they did not recognize heart disease as such Galen is said to have treated surgically an infected wound under the sternum which may have involved the pericardium Effusions were well known to the compilers of postmortem data in the sixteenth and seventeenth centuries Lower described cardiac tamponade in 1669 and Riolan (1653) followed later by Senac too advised pericardial paracentesis which was not done however so far as records go until 1819 (Romero in Barcelona) Chronic pericardial scarring was an early discovery and the first description of the special type called chronic constrictive pericarditis was apparently given by Lower in 1669 but it was not presented as a clinical entity until 1842 when Chevers of Guy s Hospital in London described it Wilks again referred to it in 1870 and finally in 1896 it was called Pick s disease after Pick who described mediastinopericarditic pseudocirrhosis of the liver Various minor signs have been attached to pericardial disease Broadbent (1895) and Ewart (1896)—see Chapter 27 Surgery for chronic constrictive pericarditis was proposed by Delorme in 1898 but not carried out until 1913 (Sauerbruch) To date hundreds of cases have now been relieved by surgery

The recognition of the types of heart disease has been of the greatest importance of all advances in the entire field of heart disease as pointed out by Cabot s classical paper The Four Common Types of Heart Disease in the *Journal of the American Medical Association* in 1914 By the early 1920 s the present day fundamental classification of cardiac diagnosis based primarily on etiology had been independently introduced and well established at the Massachusetts General Hospital in Boston and at the Bellevue Hospital in New York City The major importance of this step was indicated not only by better diagnosis prognosis and treatment but especially by directing attention to the causes of heart disease the elucidation of which will doubtless lead to effective preventive medicine so much more important in the final analysis than research interesting though it is in abnormal physiology and in therapy both medical and surgical

Congenital heart disease described in scattered reports by earlier workers was first more adequately treated as such by Farre in 1814 and by Gintrac in 1824 Peacock s book on the subject in 1858 is much better known Since then progressive advances have been made in the works of Rokitansky (1875) Abbott (1908) Laubry and Pezzi (1921) and Taussig (1947) In 1938 the present era of spectacular cardiac surgery began with the first successful closure of a patent ductus arteriosus by Gross and Hubbard al-

though Munro (1907) and others had suggested it and unsuccessful efforts had already taken place Since then other dramatic advances in surgical therapy have been made in congenital heart disease by Blalock and Taussig (1945) and by Potts (1946) in the alleviation of the tetralogy of Fallot by Crafoord (1945) and by Gross (1945) independently in the cure of coarctation of the aorta and by Gross (1945) in breaking a ring of the great vessels around trachea and esophagus *All these advances, dramatic and vital as they are* pale however in comparison with the discovery by Gregg (1941) and Swan (1943) of Australia that congenital cardiovascular defects and cataracts are likely to be found at birth in babies born of mothers who had German measles (rubella) during the first two or three months of pregnancy

Rheumatic heart disease as an entity was first suggested by Pitcairn (1788) and Baillie (1793) although valvular defects had been well described pathologically since the days of Bonetus (1679) and earlier Bouillaud in 1840 established on a firmer footing the association between rheumatic fever and heart disease Aschoff discovered his more or less specific lesion in the myocardium in 1904 and in 1913 Poynton and Paine called attention to the importance of the hemolytic streptococcus as an exciting factor confirmed by Coburn in 1931 and by others since

Subacute bacterial endocarditis was slowly separated from other heart troubles toward the end of the nineteenth century (Osler 1885) its causative *agent the Streptococcus viridans was discovered by Schottmuller in* 1910 and the disease was much studied by Libman (1910 and later) but it remained well nigh totally fatal until Loewe showed in 1944 that the majority of the cases can be cured by penicillin

Cardiovascular syphilis was probably the first etiologic type recognized Aortic aneurysms were attributed to syphilis by Pare about 1564 and aortic regurgitation with the cor bovinum was recognized as sometimes of syphilitic origin a hundred or more years ago Reuter recognized aortitis as a syphilitic lesion in 1906 Intensive antisyphilitic treatment for aortitis has been developed effectively during the present generation especially by Moore and his associates at first with the heavy metals (1932) and recently with penicillin The most important advance however has been in preventive medicine through the early recognition and specific treatment of the chancre itself or by its prevention in the first place resulting in an impressive drop now in progress in the development of aortic syphilis fifteen or twenty years after the original infection

Other infections bacterial and virus and parasitic infestations of the heart and blood vessels involve relatively few individuals nowadays in contrast to their frequency often unrecognized as such in days gone by before the control of these diseases became so impressive Diphtheria tuberculosis influenza and other virus diseases trichiniasis and trypanasomiasis (Chagas 1909 1922) have all been recognized and described by many workers often lost in history but they are now of minor import One might add however

that the first actual proof of the influenza heart did not come until 1945 (Fin land et al) in severe degree it is uncommon

Thyroid disease as it involves the heart is now no longer a problem but thirty years ago thyrotoxicosis was recognized as an important though not common cause of heart disease It was attacked successfully by surgery (sub total thyroidectomy) by Lahey and Hamilton in 1923 The introduction of speedy surgical correction of thyrotoxicosis itself and of medical measures with iodine thiouracil and irradiated iodine has practically wiped out the thyrotoxic heart The heart in myxedema was first clearly described in 1918 by Zondek it too is now very rare the disease itself having been brought largely under control

The enlarged hypertensive heart was first described as an accompaniment of nephritis by Bright himself in 1836 In 1872 Gull and Sutton called atten tion to the arteriolar fibrosis found with these enlarged hearts Both they and Bright considered that there must be present in these cases some special factor of strain although hypertension had not yet been discovered At the end of the nineteenth century blood pressure measurements in man began and soon afterward hypertension was identified It was considered as an entity separated from Bright s disease and called hyperpiesia by Allbutt in 1895 The hyper tensive heart had been serious when of high degree and not amenable to cura-tive therapy until the advent of lumbodorsal sympathectomy (Smithwick 1940) which has aided a large number of cases demonstrating finally that every single type of heart disease may be reversible (White 1944) The rice and low sodium diets have also helped some cases but something better than any of these measures is needed to control the hypertension various drugs are now being hopefully investigated in this direction especially the purified veratrum alkaloids in particular protoveratrine

The cor pulmonale (or pulmonary heart disease) has only very slowly come up for recognition The chronic type has been known for several decades (associated particularly with silicosis now under better control) but the acute cor pulmonale has only recently been described (McGinn and White 1934)

The final of the more common or important types of heart disease that due to *coronary atherosclerosis has already been referred to above in the writings* of Heberden Jenner and Herrick It remains one of the chief problems of world health today and has until the very present been much neglected in research as to etiology and pathogenesis Interesting clues have been recently uncovered however and the future looks brighter

Other causes of heart disease have been recognized for generations but only lately has their incidence been more clearly analyzed Cardiac and pericardial neoplasms have been noted on pathologic examination for centuries although at first there was great confusion in the diagnosis of the simple postmortem clots which before Kerckring (1670) were called polyp and thought to indi-cate disease In late years it has been possible even to make correct ante-

mortem diagnoses of neoplasm involving the heart and pericardium in a few cases Traumatic lesions of the heart were also recognized very early but even today in nonfatal cases they comprise one of the most difficult though fortunately uncommon aspects of heart disease Nutritional diseases involving the heart have become well recognized during the past generation especially beri beri the acceptance of which has come slowly through the work of many different individuals Somewhat similarly has been the elucidation of other rare cardiac involvement such as is discussed in Chapter 23 of this book including conditions like sarcoidosis amyloid disease hemachromatosis and lupus

Finally a few words may be added about other therapy than that mentioned above concerning specific types of heart disease that is in particular the treatment of myocardial and of coronary insufficiency and that of the arrhythmias The two most important measures of treatment of myocardial and coronary insufficiency concern two medicines which have an interesting history *Digitalis* was the Latin word coined by Fuchs from the German *Fingerhut* when he introduced that plant (the foxglove) as an afterthought in his appendix to his great herbal in 1542 From that time on for nearly two and one half centuries digitalis was officially used when it was given at all as an emetic but in a family recipe for the dropsy it held an effective though obscure place, doubtless handed down for unnumbered years until William Withering of Birmingham England in 1775 happened to be enough interested in both the practice of medicine and botany to discover through a patient of his its value in heart failure For ten years he tested it before he published his small but justly renowned monograph on the foxglove in 1785 giving credit to Fuchs for its original introduction to medical botany More than another century elapsed however before Withering s explicit and correct advice about dosage became current practice During that century efforts were made to purify the crude drug and one hundred years ago Nativelle (1847) in France made digitoxin (digitaline Nativelle) which has very be latedly become popular in the U S A Many preparations of digitalis are now available and effective meanwhile the dried leaves themselves remain a cheap and useful medicine too In recent years there has been a tendency to give more of the drug both in distribution and in quantity than needed in contrast to its neglect for well over a century after Withering

The second notable medicine is nitroglycerine (glyceryl trinitrate) invaluable in the treatment of periodic and frequently recurring coronary insufficiency in the form of angina pectoris Preceded for a few years by amyl nitrite (Brunton 1867) it was introduced by Murrell in 1879 to take the place of the much less effective and less practical employment of spirituous liquor originally suggested by Heberden himself in 1768 There is today no better measure The most important advance in its use in recent years has been its employment prophylactically, making more comfortable and safer the undertaking of certain necessary or unavoidable strains

In the control of arrhythmias quinidine has already been mentioned It was introduced by Frey in 1918 to control atrial fibrillation four years after

a patient of Wenckebach had rediscovered the helpfulness of quinine referred to a century and a half earlier by Senac (1749) The other most important therapy of arrhythmia has been that of the effect of epinephrine parenterally in the control of Adams Stokes attacks (Hardoy and Houssay 1917 Phear and Parkinson 1922)

Many other drugs have of course been used in the treatment of heart disease from time immemorial but brief mention may be added here simply of two Mercury was employed centuries ago not only in the therapy of syphilis but also as a diuretic and like bloodletting for almost any disease in fact one poor girl with active rheumatic fever seriously ill at the Massachusetts General Hospital in 1846 was made miserable by the large doses of mercurial and many other drugs the use of which was the custom of the day However it was not until Saxl in Vienna in 1920 accidentally discovered the more favorable effect of mercury given parenterally rather than by mouth that this currently important diuretic has come into its own The other medicine which may be mentioned as an alleviator of misery though not a cure of heart disease is salicylic acid and its salts originally obtained from the bark of the swamp willow near the site where rheumatism itself was supposed to have been engendered The salicylates have been used for generations to assuage the pains of acute rheumatic fever and as a matter of fact of other diseases such as rheumatoid arthritis for this purpose it has an essentially specific effect though the myocardial and endocardial manifestations of rheumatic fever are not appreciably helped And now on the horizon there are appearing the important hormones ACTH and cortisone which give promise of controlling these diseases which involve the joints heart valves and connective tissues

In closing this chapter a comment may be added about the history of diet as it applies to heart disease In general apparently for centuries advice has been given to individuals with cardiac symptoms and signs to eat lightly and of simple foods Mackenzie for example in his volume on *Heart Disease* published in 1908 advised small meals of whatever easily digested foods the patient himself preferred The two important advances that have come have both been rather recent first the addition of vitamins as needed especially when there is malnutrition often resulting from chronic heart failure on which occasion vitamin B complex and other vitamins (though not specifically vitamin E) have been helpfully added during the last generation The much more significant advance however has been the belated recognition of the importance of a low sodium intake in the presence or under the threat of congestive heart failure with accumulation of fluid in lungs liver extremities or elsewhere in the body A proper application of the helpful effect of a low sodium intake in the diet has been one of the great advances during the last decade However the beginning of this dates back doubtless even before Karell in 1866 advised a very restricted milk diet consisting of only 800 cc of skimmed milk a day Almost certainly the chief value of this diet lay in the restricted sodium rather than in the restricted fluid intake In 1903 Widal and Lemierre were the first clearly to show that it was the salt itself that was im-

portant Allen in 1920 had used a low salt diet for hypertension and some of his cases with congestive failure were particularly benefited It has however been Barker in 1932 Schroeder in 1941 and Schemm in 1942 who presented convincing data of the effect of decreased intake of sodium in congestive heart failure One other diet may be mentioned because of its wide spread use in the treatment of hypertension and that is the rice diet of Kempner (1944) This diet low in protein and fat as well as in sodium has helped some patients with hypertension The mechanism of its action has not been clarified It is still under investigation

In this chapter I have attempted briefly to present the trends of advance in our knowledge of cardiovascular disease but we still have more to learn in our campaign to reduce the incidence of heart disease by preventive measures than we have already learned during all the ages that have gone before

AN OUTLINE OF THE EVOLUTION OF OUR KNOWLEDGE OF THE HEART AND ITS DISEASES[1]

(Important contemporary events are to be found at *the right side of the page in bold face type*)

B C

Imhotep (Egypt) 2980 B C and successors Observation of the pulse

Hippocrates (Greece), 460 B C Treatises containing description and prognostic significance of symptoms and signs, including dyspnea and dropsy

Aristotle (Greece) 384 B C Pulsation of the chick embryo s heart

Erasistratus, Herophilus (Alexandria) 310 B C Anatomy of the human heart

A D

Celsus (Rome) earliest years of first century A D *De Re Medicina* including recommendation of venesection for severe dyspnea

Dioscorides (Greek working in Rome) *De Medicinali Materia* including the diuretic squill 60 A D

** **Galen** (Greek working in Rome) 131 Detailed study of the pulse

Hotel Dieu Paris, 651
The Crusades
Medical School at Salerno 1000
St Bartholomew s Hospital, 1123
Bologna University 1156
Montpelier University 1180
Oxford University 1201
The Inquisition thirteenth century
Magna Carta 1215
Cambridge University 1223
Sorbonne University 1257
Al Mansur Hospital at Cairo 1283

[1] A single asterisk indicates important entries and double asterisks the more important entries in the historical table

Ibn Nafis (Egypt) Pulmonary circulation 1300

The Renaissance fourteenth and fifteenth centuries
The Black Death 1348
Invention of Printing 1440

Leonardo da Vinci (Italy), 1452 Drawings of the heart

Constantinople captured by the Turks 1453
Martin Luther 1483–1546
Discovery of America 1492

Benedetti (Italy) Case of malposition of the heart 1493

HEART DISEASE NOT YET RECOGNIZED

1500

** Benivenio (Italy) *De Abditis Nonnullis ac Mirandis Morborum et Sanationum Causis* some of the earliest autopsy proof of the existence of heart disease including cases of endocarditis and fibrinous pericarditis 1507

Berengario da Carpi (Italy) Commentary on the anatomy of Mondino (1516) with mention of a dilated heart 1521

Botallo (Italian working in France) 1530 Description of the ductus arteriosus (Botalli)

Canano (Italy) Valves in veins 1540

Mexico City Hospital 1524

** Vesalius (Belgian working in Italy) *De Fabrica Humani Corporis* 1543 with description of human heart Also antemortem recognition of aortic aneurysm *1555 confirmed at autopsy two years later*

* Servetus (Spaniard working in France and Italy) Mention of the pulmonary circulation in his religious tract *Restitutio Christianismi* 1553

* Colombo (Italy) Description of the pulmonary circulation in *De Re Anatomica* 1559

* Fernel, * Pare (France) Aortic aneurysm ascribed to syphilis — *Medicina* 1554; Surgery 1564

* Caesalpino (Italy) Introduction of term circulation with reference to movement of blood in arteries and veins, 1559

Schenck (Germany) *Observationum Medicarum Rarum* 1584 Important compilation of case records based on symptoms

1600

Fabrizio d Acquapendente (Italy) *De Venarum Ostiolis (Venous Valves)* 1603 Creation of the anatomical theater at Padua

Albertini (Italy) *De Affectionibus Cordis* 1618 The first extensive treatise on the heart but with little important information largely a review of ancient and medieval theories with long discussion of palpitation and syncope

The Thirty Years War, 1618–1648

Aselli (Italy) Discovery of lacteal vessels 1622

** **Harvey** (Englishman studying in Italy) *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus* 1628 Proof of the circulation of the blood

The Commonwealth (Cromwell) in England 1649–1660

Pecquet (France) Description of the receptaculum chyli and thoracic duct 1651

Bartholin (Denmark) Discovery of lymph vessels 1653

Malpighi (Italy) *De Pulmonibus* containing a note on the discovery of capillaries 1661

Plague in London 1666
Great fire of London 1666

** **Lower** (England) *Tractatus de corde* 1669 This includes the experimental proof that dropsy may result from venous obstruction

** **Kerckring** (Holland) *Spicilegium anatomicum* 1670 Recognition that postmortem clots in the heart are not polyps or worms their faulty interpretation had caused confusion for centuries

* **Mayow** (England) *Tractatus duo* 1668 and *Tractatus quinque* 1674 Demonstration of the function of breathing to change venous blood to arterial blood by interchange of gases the blood taking up the nitro-aerial spirit of the air in the lungs

* **Stensen** (Denmark) First description of the tetralogy of Fallot 1672

** **Bonet** (France) *Sepulchretum* 1679 Storehouse of case reports with autopsies containing many instances of cardiovascular disease such as that of the Parisian tailor who dropped dead in the street and showed post mortem a calcified stenosed aortic valve

Siege of Vienna 1683
Peter the Great (Russia) 1689–1725

1700

Cowper (England) Plate showing aortic stenosis 1705

Floyer (England) *Physician s Pulse Watch* 1707 Recommendation of the recording of the pulse rate in health and disease

** **Vieussens** (France) *Traite du cœur* 1715 Description of coronary circulation Thebesian vessels (Thebesius 1716) and a few abnormalities of the heart including mitral stenosis and dyspnea therefrom

Albertini Hippolito (Italy) Cardiac palpation as an aid to diagnosis 1726

** Lancisi (Italy) *De Motu Cordis et Aneurysmatibus* 1728 Discussion of cardiac and aortic enlargement and description of engorgement of neck veins with dilatation and failure of the right ventricle Also *De Subitaneis Mortibus* 1707 The first treatise on sudden death with autopsy findings in five cases

* Hales (England) *Hæmasaticks* 1733 First study of blood pressure

** Senac (France) *Traite du cœur* 1749 Important textbook on the heart including observations on congenital defects and the use of quinine for rebellious palpitation

Munro (England) Treatise on dropsy 1755

** Morgagni (Italy) *De Sedibus et Causis Morborum* 1761 Extensive discussion of pathology with many cardiovascular observations including calcification of the coronary arteries

** Auenbrugger (Austria) *Inventum Novum* 1761 Introduction of mediate percussion in the study of heart size and of pericardial and pleural effusions

** Heberden (England) Angina pectoris 1768

** Neubauer (Germany) Cardiac nerves 1772

Lavoisier (France) Respiratory gas exchange 1777

Sandifort (Holland) Early description of tetralogy of Fallot 1777

U.S.A., 1783

** Withering (England) *An Account of the Foxglove* 1785 Introduction of digitalis in the treatment of dropsy

* Parry (England) Thyrotoxicosis and its effect on the heart 1786

Pitcairn (England) Rheumatism of the heart 1788

French Revolution 1789

Baillie (Scotland) *Morbid Anatomy* 1793 Description of endocarditis

** Jenner (England) The relationship of angina pectoris to coronary disease presented in a letter published by Parry in his *Syncope Anginosa* 1799

1800

Scarpa (Italy) Arteriosclerosis 1804 He also gave an excellent description of the nerves of the heart in his *Tabulæ Nevrologicæ* in 1794

* Corvisart (France) *Maladies du Cœur* 1806 Important textbook on the heart He also restored Auenbrugger's percussion as an important method of examination 1808

Burns (Scotland) Angina pectoris due to myocardial ischemia Textbook on diseases of the heart 1809

Wells (U S A) Cardiac rheumatism 1810

* Testa (Italy) *Malattie del cuore* 1810

Farre (England) Cardiac malformations including the tetralogy of Fallot 1814

* **Hodgson** (England) *Treatise on the Diseases of Arteries and Veins* 1815

Kreysig (Germany) Textbook on heart diseases 1815

* **Cheyne** (Ireland) First good description of Cheyne Stokes breathing 1818

** **Laennec** (France) *De l Auscultation Mediate* 1819 Introduction of the stethoscope

Romero (Spain) Pericardial paracentesis 1819

Gintrac (France) Maladie bleue (morbus caeruleus), 1824

* **Adams** (Ireland) Classic description of the Adams Stokes syndrome 1827

Hodgkin (England) Aortic insufficiency 1827

Andral (France) Pulmonary arteriosclerosis 1829

* **Hope** (England) *A Treatise on Diseases of the Heart and Great Vessels* 1832 containing a description of left ventricular failure with pulmonary vascular congestion and cardiac asthma

* **Corrigan** (Ireland) Aortic insufficiency, 1832 The Corrigan pulse

Lobstein (France) Arteriosclerosis 1833

Williams C J B (England) *The Pathology and Diagnosis of Diseases of the Chest* 3rd edition 1835 Description of the mitral diastolic murmur, among other murmurs

Bouillaud (France) *New Researches on Acute Articular Rheumatism* (with its relationship to acute and chronic endocarditis and pericarditis) 1836

** **Bright** (England) Association of heart disease with kidney disease 1836

Magnus (Germany) Respiratory function of the blood 1837

* **Skoda** (Austria) Treatise on percussion and auscultation 1839

* **Purkinje** (Bohemia) End branches of the atrioventricular bundle—the Purkinje fibers 1839 He also described the visual toxic effects of digitalis

* **Chevers** (England) Description of chronic constrictive pericarditis 1842

* **Hall** (England) Sudden death due to arrest of coronary circulation 1842

* **Weber Brothers** (Germany) Vagal inhibition of the heart 1845

Nativelle (France) Introduction of digitoxin (digitaline) 1845

* **Hutchinson** (England) Introduction of the determination of the vital capacity of the lungs 1846

* **Ludwig** (Germany) Introduction of the graphic method 1847

1850

Bernard (France) Vasomotor nerves 1851

Stannius (Germany) Heart block 1852

Kirkes (England) Peripheral embolism from valvular vegetations 1852

* **Stokes** (Ireland) Textbook on heart disease 1854

* Kölliker and Müller (Germany) Cardiac electricity 1855
* Vierordt (Germany) Sphygmography introduced 1855

Virchow (Germany) Thrombosis and embolism 1856

Peacock (England) *Malformations of the Heart* 1858

Foster (England) Rhythmicity of the heart 1859

Marey (France) Sphygmograph 1860

Duroziez (France) Vascular murmurs of free aortic regurgitation 1861

Flint (U S A) The murmur of relative mitral stenosis 1862

* Raynaud (France) Vasoconstriction in the hands 1862

Karell (Russia) Restricted diet in heart failure 1866

* Kussmaul (Germany) Periarteritis nodosa 1866 Pulsus paradoxus 1873

Brunton (England) Amyl nitrite introduced for angina pectoris 1867

* Fick (Germany) Blood flow studies 1870
* Da Costa (U S A) Irritable heart of soldiers 1871
* Traube (Germany) Description of alternation of the pulse and of cardiorenal disease 1872

** Gull and Sutton (England) Arteriocapillary fibrosis 1872

Welch F H (England) Differentiation of aortic syphilis from aortic atheroma 1875

Rokitansky (Austria) Septal defects 1875

Southey (England) Tubes for anasarca 1877

Welch W H (U S A studying in Germany) Acute pulmonary edema 1878

** Sanderson and Page (England) Study of heart action by capillary electrometer 1878

Rosenbach (Germany) Cardiac reserve 1878

Roger (France) Murmur of interventricular septal defect 1879

* Murrell (England) Nitroglycerine introduced in treatment of angina pectoris 1879

Winiwarter (Germany) Endarteritis 1879

Barie (France) Traumatic lesions of the heart valves 1880

* von Basch (Germany) Introduction of the sphygmomanometer 1881

Gaskell (England) Heart block 1881

Steell (England) Murmur of functional pulmonary regurgitation 1881

Concato (Italy) Polyserositis 1881

Leyden (Germany) Coronary artery disease 1884

Osler (Canada U S A and England) Bacterial endocarditis 1885

* Waller (England) Human electrocardiography 1887
* Bristowe (England) Paroxysms of tachycardia 1887

Fallot (France) Congenital heart disease—Fallot s tetralogy 1888

* Bouveret (France) Paroxysmal tachycardia 1889
* Riva Rocci (Italy) Development of sphygmomanometer 1891

Kent (England) }
His (Germany) } Atrioventricular bundle 1893

Bayliss and Starling (England) Electrocardiographic studies 1893

* **Einthoven and Geluk** (Holland) Phonocardiography 1894
Allbutt (England) Hyperpiesia 1895
Broadbent (England) Pericarditis 1895
Ewart (England) Signs of pericardial effusion 1896
Porter (U S A) Coronary circulation 1896
* **Marie** (France) Myocardial infarction 1896
Farina (Italy) and Rehn (Germany) Operations on the heart 1896
Pick (Germany) Chronic mediastinopericarditic pseudocirrhosis of the liver 1896 Chronic constrictive pericarditis first described by Chevers in 1842
* **Williams** (U S A) Roentgen ray study of the heart 1896 Roentgen introduced the new ray in 1895
* **Delorme** (France) Pericardial resection suggested 1898
Gibson (Scotland) Textbook on heart disease 1898
Fiedler (Germany) Interstitial myocarditis 1899

1900

** **Mackenzie** (Scotsman working in England) *The Study of the Pulse* 1902
* **Moritz** (Germany) Orthodiagraphy of the heart 1902
Brauer (Germany) Precordial rib resection 1902
Carrel (Frenchman working in U S A) Arterial suture 1902
Matas (U S A) Aneurysmorrhaphy 1902
** **Einthoven** (Holland) Introduction of the string galvanometer for electrocardiography 1903
* **Wenckebach** (Hollander working in Germany and Austria) Arrhythmia of the heart 1903
* **Widal and Lemierre** (France) Low sodium intake for congestion 1903
** **Aschoff** (Germany) Myocardial lesions in rheumatic fever 1904
Pal (Austria) Vascular crises 1905
* **Kohler** (Germany) Teleroentgenography 1905
* **Korotkow** (Russia) Auscultatory sphygmomanometry 1905
Romberg (Germany) Textbook on heart disease 1906
Reuter (Germany) Demonstration of spirochaeta pallidum in aorta in syphilitic aortitis 1906
Keith and Flack (England) Discovery of the sinoatrial node 1907
Tawara (Japanese working in Germany) The atrioventricular node and its connection with the bundle its branches and the network of Purkinje fibers 1908
Buerger (U S A) Thromboangiitis obliterans 1908
Abbott (Canada) Congenital defects 1908
Trendelenburg (Germany) Pulmonary embolectomy 1908
Pachon (France) Oscillometry, 1909
* **Rothberger and Winterberg** (Austria) Atrial fibrillation recognized clinically 1909

*Lewis (Welshman working in England) Atrial fibrillation recognized clinically independent observation 1909 Blood vessels of the skin 1927

Schottmuller (Germany) Identification of the Streptococcus viridans as the cause of subacute bacterial endocarditis 1910

*Lian (France) Left and right sided heart failure 1910

Hirschfelder (U S A) Textbook on heart disease 1910

Libman (U S A) Subacute bacterial endocarditis 1910

*Ritchie (Scotland) Atrial flutter 1911

**Herrick (U S A) Clinical recognition of coronary thrombosis 1912

Anitschkow (Russia) Atherosclerosis 1912

Krogh and Lindhard (Denmark) Blood flow 1912

Sauerbruch (Germany) Pericardial resection 1913

**Cabot (U S A) Etiology of heart disease 1914

World War I, 1914–1918

Cohn (U S A) Digitalis effect on *T* wave of the electrocardiogram 1915

Eggleston (U S A) Digitalis dosage 1915

Jonnesco (Roumania) Sympathectomy for angina pectoris 1916

*Oppenheimer, et al (U S A) Neurocirculatory asthenia 1918

*Smith (U S A) Coronary electrocardiogram 1918

Levine and Tranter (U S A) Myocardial infarction 1918

*Frey (Germany) Introduction of quinidine in the treatment of atrial fibrillation 1918

Zondek (Germany) The heart in myxedema 1918

Christian (U S A) Digitalis in normal rhythm 1919

Pratt (U S A) Digitalis strength 1919

Wyckoff (U S A) Classification of cardiac diagnosis 1919

Specialization

*Pardee (U S A) Coronary *T* waves of the electrocardiogram 1920

**Saxl (Austria) Mercurial diuretic injections 1920

Rehn (Germany) Pericardial resection 1920

Reid (U S A) Effect of arteriovenous fistula on heart 1920

Gross (Canada) Coronary artery injections 1921

Vaquez (France) Textbook on heart disease 1921

*White and Myers (U S A) Classification of cardiac diagnosis 1921

Krogh (Denmark) Capillary physiology 1922

Key (Sweden) Embolectomy 1922

Chagas (Brazil) Cardiac trypanosomiasis 1922 (1909)

Scott (U S A) Quinidine for ventricular paroxysmal tachycardia 1922

Plummer (U S A) Iodine in the initial treatment of thyrotoxicosis 1923

Hering (Germany) Carotid sinus reflex 1923

American Heart Association established 1924

* **Hamilton and Lahey** (U S A) Cure of thyrocardiacs by subtotal thyroidectomy (the first clear demonstration of the reversibility of heart disease) 1924
Schmieden (Germany) Pericardial resection 1924
Cutler (U S A) Valvulotomy 1924
Parkinson (England) Epinephrine in Adams Stokes attacks 1924
Rowntree and Adson (U S A) Bilateral lumbar sympathectomy for hypertension 1925
Mandl (Austria) Paravertebral nerve injection for angina pectoris 1925
Cannon (U S A) Accessory cardiac nerves Discovery of sympathin from the thoracic sympathetic chain 1926
Blumgart and Weiss (U S A) Velocity of blood flow 1927
Wenckebach and Aalsmeer (Holland) Beriberi heart 1928
* **Keefer and Resnick** (U S A) Angina pectoris 1928
Keith et al (U S A) Malignant hypertension 1928
Weber (Czechoslovakia) Electrocardiogram in familial periodic paralysis associated with potassium lack, 1928
Erdheim (Austria) Medionecrosis aortae idiopathica 1929
von Gierke (Germany) Glycogenic visceral enlargement 1929
* **Forssmann** (Germany) Cardiac catheterization 1929 angiocardiography 1931
Edens (Germany) Textbook on heart disease 1929
Churchill (U S A) Pericardial resection 1929
Laubry (France) Textbook on heart disease 1930
* **Wilson** (U S A) Bundle branch block 1930 Direct and chest leads in electrocardiography 1930–1936
Grant (Scotsman working in England) Arteriovenous anastomoses 1930
Coburn (U S A) Hemolytic streptococcus infection and rheumatic fever 1931
* **Wood and Wolferth** (U S A) Precordial leads in coronary occlusion 1932
Manca (Italy) Virus myocarditis (mumps) 1932
Blumgart Levine and Berlin (U S A) Total thyroidectomy for angina pectoris and heart failure 1933
Goldblatt (U S A) Hypertension produced by renal ischemia 1934
Shennan (England) Dissecting aortic aneurysms 1934
Leary (U S A) Coronary atherosclerosis 1935
Beck (U S A) Pericardial implantation of pectoral muscle to bring new blood vessels to the heart seriously affected by coronary disease 1935
* **McGinn and White** (U S A) Acute cor pulmonale 1935
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PART I

CARDIOVASCULAR EXAMINATION SYMPTOMS and SIGNS

CHAPTER 2

THE RANGE OF THE NORMAL HEART

Six years have elapsed since this chapter was written as a useful introduction to this volume few changes in it have been necessary since in this interval of time little has been added to our knowledge of the range of the normal heart despite the great interest and importance of the subject occasioned by the examination of many hundreds of thousands of healthy young men for military service

It is requisite that every intelligent Patient should try his Pulse in a Morning in his Health that he may inform his Physician what number of Pulses he has in a perfect Health by which a Physician may judge of his natural Constitution and the Physician may know how far the diseas d Pulse receeds from the natural Numbers and whether the Numbers of the Pulse are increas d or be deficient by which he may discern whether tis a hot or a cold disease so wrote Sir John Floyer in 1707 in the *Pulse Watch*

The words I have just quoted make up one of the rare examples in medical literature old or new not only of the recognition of the wide range of bodily measurements and functions of humankind in health but what is still more important also of a relatively simple and accurate method of determining changes denoting abnormality in any given individual thus avoiding the many clumsy and inaccurate measures that have been devised for general use

The range of the normal heart remains today in cardiovascular physiology one of the most difficult problems accurately to assess and in the diagnosis of cardiovascular disease one of the most important and yet neglected sub jects It is astonishing to find relatively so little written about it in works on medicine by either ancient or modern authors As a matter of fact the ancients actually paid more attention to the problem than have the moderns largely without doubt because they had to do so since they didn t even recog nize the existence of heart disease Galen Avicenna and other authorities of the classical and medieval ages tried for example in their analysis of the pulse which is as far as they got in cardiology to explain all variations on the basis of age sex temperaments (hot cold moist and dry) seasons of the year climate locality food and drink sleep and waking athletic exercise

pregnancy pain disease elsewhere in the body and emotional states (anger delight, joy grief and fear) Under the circumstances they did an extraordinarily good job in showing how all of these conditions may affect the pulse many of us today might profitably take a leaf from their book

In the sixteenth century the pendulum began to swing back a little when autopsies revealed through the findings of chronic heart lesions the fact that the heart could be diseased and yet life continue Gradually as more and more evidence of the frequency and multiplicity of heart disease was discovered the impetus of the backswing of the pendulum accelerated through the centuries until it reached its maximum (we hope) early in the nineteenth century with such authorities as Corvisart Napoleon s physician He asserted that heart disease was with the single exception of pulmonary tuberculosis one hundred times the most common of all organic diseases in France both in public and in private practice He thought the majority of cases of asthma hydrothorax and various other conditions were the result of heart disease and that cardiac fatalities were very likely more numerous than deaths due to lesions of brain stomach liver kidneys and other organs combined He even scorned the idea of the need of statistical proof for these remarks He attributed the frequency of heart disease to the hard or rather constant work of the heart and to the passions of mankind

Just thirty years later however in 1836 John C Williams of Edinburgh wrote a book on Practical Observations on Nervous and Sympathetic Palpitation of the Heart Particularly as Distinguished from Palpitation the Result of Organic Disease (Figure 1) He deplored the frequency with which functional derangement of the heart was attributed to heart disease itself and brought the pendulum a wee bit back from the extreme swing the reverse of Galen s for which Corvisart and others of that day and since were responsible He wrote that *palpitation* was

> frequently by a careless observer regarded as symptomatic of some serious organic or structural change being established either in the coverings of the heart its muscular texture or in some of its valvular appurtenances A careful and deliberate inquiry however he went on to say "will in the generality of cases enable us to strip them of their apparent obscurity and danger and reduce them to their true place in nosological arrangement Latterly there has been too great a rage for tracing diseases almost exclusively to *vascular derangement* I deprecate this because I am convinced of the unceasing influence of the nervous system both in health and in disease A deservedly popular writer on medicine of the present day says The longer we live the more we see and the deeper we study so much the more shall we become convinced that not only are the primary impressions of morbific causes sustained by the sentient system of the human fabric but it is here the primary morbid movements first begin and are thence propagated to the vascular apparatus which from that moment re acts upon and is again influenced by the nervous system No man I am satisfied can ever be a sound Pathologist or a judicious practitioner who devotes his attention to one of these systems in preference or to the exclusion of the other through life they are perpetually acting and inseparably linked together

PRACTICAL OBSERVATIONS

ON

NERVOUS AND SYMPATHETIC

PALPITATION OF THE HEART,

PARTICULARLY AS DISTINGUISHED FROM

PALPITATION

THE RESULT OF ORGANIC DISEASE

TO WHICH ARE PREFIXED SOME GENERAL REMARKS ON THE

USE OF THE STETHOSCOPE

AND

EMPLOYMENT OF PERCUSSION

IN DIAGNOSIS OF DISEASES OF

THE HEART AND LUNGS

BY JOHN CALTHROP WILLIAMS, M D

EDINBU GH

PHYSICIAN TO THE NOTTINGHAM DISPE SARY AND TO THE NOTTINGHAM UNION HOSPITAL AND DISPENSARY LECTURER ON THE PRINCIPLES AND PRACTICE OF PHYSIC EXTRAORDINARY MEMBER OF THE ROYAL MEDICAL SOCIETY EDINBURGH

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LONDON

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NOTTINGHAM J HICKLIN JOURNAL OFFICE

1836

FIG 1 Title page of book by John C Williams 1836 on nervous and sympathetic palpitation of the heart

Williams also quoted the late eminent Dr Baillie as follows

"There are in truth few phenomena which puzzle perplex and lead into error the inexperienced (and sometimes the experienced) practitioner so much as in ordinate action of the heart He sees or thinks he sees some terrible cause for this tumult in the central organ of the circulation and frames his portentous diagnosis and prognosis accordingly In the pride of his penetration he renders miserable for the time the friends—and by his d reful countenance damps the spirits of his patient But ultimate recovery not seldom *disappoints* his fears and the Physician is mortified at his own success

Finally Williams presented several case reports the most striking of which was that described by Morgagni of a boarding mistress who had palpitation She was bled with some appearance of relief The palpitation returned and so she was bled again daily until she died Nothing abnormal was found at autopsy in thorax or abdomen and Morgagni wrote

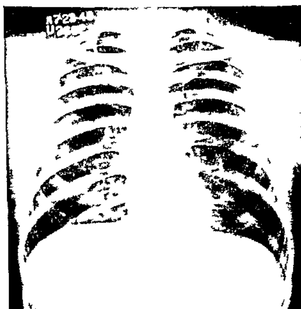
It would have been well had her physician remembered that the very name of Palpitatio Cardiaca implies a course of proceeding quite the reverse

Like the rest of the body the heart varies in size and shape and action from one person to another somewhat according to sex and age and body size Even when we take into careful consideration these three factors however the range of the normal heart is too wide for us to know whether or not there has been some slight enlargement from strain or infection or otherwise or some slight change in shape or a change in action in almost any given case This is true even of postmortem measurements of weight and volume and shape and all the more so of clinical findings by physical examination or by x ray electrocardiographic and physiologic measurements of the circulation (Figure 2) I do not mean that this difficulty should prevent us from constructing and utilizing tables based on our present knowledge but we should clearly recognize their inadequacy and seek better correlative factors than we have at our disposition to date Body build, aside from size largely a family inheritance is unquestionably of great importance and yet we have largely neglected it Other bodily measurements besides height and weight and surface area need evaluation We have found for example that the hearts of identical twins resemble each other closely on physical examination and by x ray study and electrocardiography although it is still possible to distinguish by minor details the electrocardiogram of one twin from that of the other

Moreover in a given person one must use great judgment in comparing the findings from day to day or hour to hour based on clinical examination The height of the diaphragm is of the greatest importance especially in the analysis of x ray films and electrocardiograms (Figures 3, 4 and 5) it changes constantly not only with ordinary breathing but with the amount of food or air in the stomach the bulk of the contents, solid or gaseous of the intestines the enlarging uterus in pregnancy the addition of fat which is so



A



B

FIG 2 A comparison of the appearance of the heart shadows in roentgenograms of two individuals without heart disease who died noncardiac deaths and who showed at autopsy heart weights of 200 grams each without any evidence of cardiovascular abnormalities

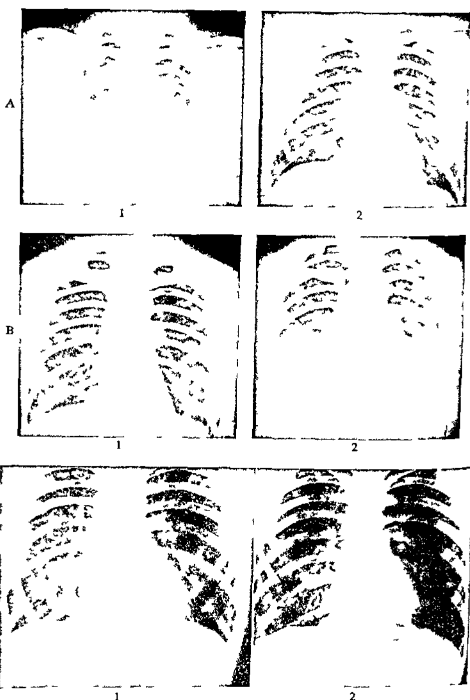
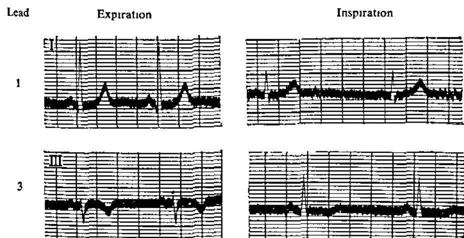


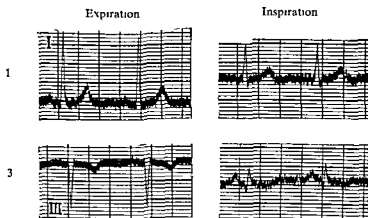
FIG 3 Roentgenograms of the thoraces of normal young men showing the effects on the heart shadows of alteration of the level of the diaphragm in respiration (*A*) Short stocky physician (1) during quiet breathing in upright position (2) at height of full inspiration in upright position (*B*) Slender young physician (1) during quiet breathing in upright position (2) at height of full expiration in upright position Note the similarity of *A*1 and *B*2 and of *A*2 and *B*1

(*C*) B W male age 27 (1) Normal control deep inspiration immediate exposure T D 14 6 cm height of diaphragm 13 1 cm (2) Effect of Valsalva s experiment deep inspiration followed by forced expiration against 40 mm Hg for 5 second T D [illegible] cm height of diaphragm 12 4 cm T D = transverse diameter of heart

often deposited in the abdomen or in its wall certain intra abdominal diseases particularly resulting in enlargement of liver or spleen ovarian cyst or ascites diaphragmatic herniation and finally with certain intrathoracic diseases especially those that cause an extreme pulmonary emphysema with deep lowering and little motion of the diaphragm It is often not realized that the prolonged fixation of the diaphragm at the level of full held inspiration (simu lating the Valsalva experiment) results in an appreciable decrease in the size of the x ray heart shadow (Figure 3C) this can result in erroneous estima



A



B

FIG 4 Electrocardiograms (Leads 1 and 3) from two normal individuals (*A*) and (*B*) showing the effect of deep expiration and inspiration on the deviation of the electrical axis

tion of heart size if roentgen studies of the lungs are used for cardiac appraisal (see Chapter 7)

Besides the height of the diaphragm the position of the body itself makes a difference (Figure 6) One should always stipulate therefore whether an examination physical x ray or electrocardiographic is made in the upright position or recumbent In our own cardiographic laboratory years ago w

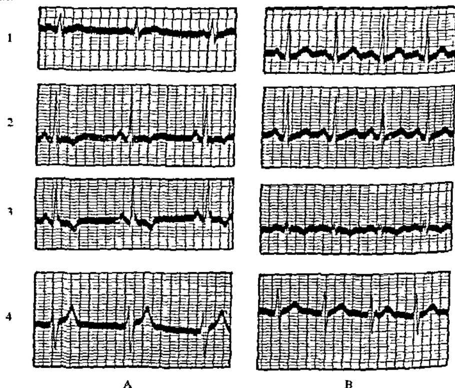
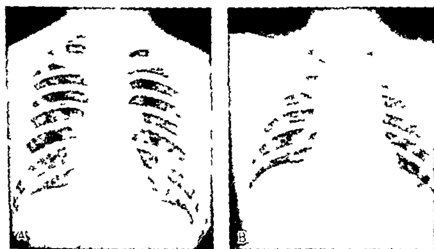


FIG 5 Electrocardiographic changes (4 leads) with respiration in normal healthy man of stocky build (*A*) At height of full inspiration (*B*) At height of full expiration Lead 4 was taken with exploring electrode over the fifth intercostal space at the lef midclavicular line and the remote electrode on the left leg (Graybiel and White *Electrocardiography in Practice* W B Saunders Company Philadelphia 1941 Figures 16 and 17)

didn t record the position although the tracings were almost always made with the patient sitting comfortably In the last ten years however since we found *what a difference position may (though it usually does not) make* we have recorded by a simple straight line the angle of the patient s body Po i tions of diaphragm and of body influence not only the anatomic and electric angle of the heart in the frontal plane but result in a rotation which is also important in its effects though not so easy to measure

The immediate state of health is another vital factor frequently influencing the heart findings on examination A heart perfectly normal to start with

and even later on showing normal myocardium endocardium valves and pericardium at autopsy may dilate acutely or subacutely from the effect of severe hypochromic anemia massive pulmonary embolism (to produce the acute cor pulmonale) and paroxysmal tachycardia at excessive rates as for example in the case of infants where the heart rate may reach 300 or more a minute and result not only in general cardiac dilatation but also in con gestive failure with engorgement of the liver Some of these infants have been erroneously diagnosed as having the so-called idiopathic hypertrophy of the heart and some have been wrongly regarded as abdominal emergency



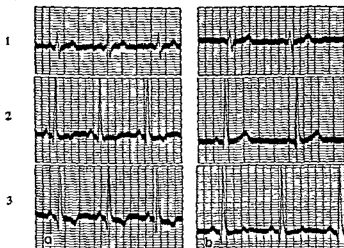


FIG 6 Roentgenograms of the thorax of a healthy young man (above) and electrocardiograms (limb leads) of another healthy young man (below) both slender in build showing the effect of change in body (and heart) position—(*A* and *a*) sitting upright (*B* and *b*) lying supine

cases for example pyloric stenosis because of the vomiting caused by the acute congestive failure Severe infectious diseases may also alter the presumably normal cardiac findings on examination without producing actual heart disease Acute rheumatic infection can of course precipitate acute or subacute cardiac dilatation and failure from the rheumatic myocardial disease, and diphtheria may seriously affect the myocardium but leaving these two specific infections out there are still other infections like pneumonia which may cause temporary systolic murmurs and even electrocardiographic changes especially in rapidly growing or delicate individuals Whether these murmurs are to be ascribed always to slight dilatation or how much the speeding up of blood flow has to do with them we don t know It is clear however that thyrotoxicosis without producing actual heart disease in the acute cases can alter the findings on examination of the heart not only in producing a tachycardia and increased pulse pressure but by the increased pulmonary blood flow causing marked accentuation of a physiologic pulmonary systolic murmur and a bulging of the pulmonary arc in the x ray picture simulating a mitral shape of heart shadow

How much the factor of physical strain is responsible for changes in heart size and shape in man we don t know Once upon a time the medical profession as well as the laity talked glibly of the athletic heart When most athletic hearts were shown to be something else the term went into the discard and now we doctors say almost as glibly that there is no such thing as an athletic heart However a revision of the past and present opinions is still awaited on the basis of most careful studies not yet adequately assembled There is a hint from several sources including an annual appraisal of Harvard *oarsmen which was for some years conducted by various associates of mine* that an occasional or more likely a rare person may after some years of excessively strenuous sport develop an increase in heart size out of keeping with any increase in body size This sort of change is reasonable to expect in view of experimental evidence in animals where it has been shown that long-continued physical exercise produces hearts that are distinctly larger than those of animals kept very quiet and in view of the well known fact that hares have relatively very much larger hearts than have rabbits racing greyhounds than other dogs and race horses than ordinary mounts Exercise can of course produce transient systolic murmurs mostly in the pulmonic area or increase those already present even in normal persons Another point of interest is that a trained athlete tends to have a slow pulse or one that slows quickly after exercise although I can well remember counting the pulse rate of the winner of a marathon race a few years ago and finding it faster (118) at the starting line before he had taken a step than at the finish (110) after running 26 miles in his case nervous tension as to the outcome of the race was doubtless responsible acting like stage fright I would hasten to add *however that there is no* evidence that vigorous exercise in the case of a healthy person in good training hurts the heart If anything the reverse is true as pointed out by Morgan in a volume entitled *University Oars* published by

Macmillan in London in 1873 in this book data are presented which indicate that the Cambridge and Oxford oarsmen of a hundred years or more ago outlived their expectation It may well be that the change to a very sedentary life is more harmful than a maintenance of exercise

The effect of high altitude on the heart and circulation is in rare individuals an important consideration Not many persons have exposed themselves to altitudes of 12 000 feet or more as permanent residents or even temporarily but now of course with the circulatory adjustments in aviators especially in military service the problem has become acute Circulatory collapse probably antedates serious cardiac involvement itself in mountain climbers and in aviators in the latter either from the effect of low oxygen tension in the atmosphere or from the centrifugal force of great speed and change in direction or from still other factors Residents at very high altitudes do however show circulatory adjustments that have been well described and resemble somewhat those in the cyanotic type of congenital heart disease at sea level Tandler has pointed out incidentally that the bird Lagopus living in the Alps has a heart weight 50 per cent greater than that of the Lagopus of the same size living at lower altitudes

The factor of the effect of rapid growth on cardiac findings has not yet been completely assessed It is the impression of many of us that a fast growing boy or girl or indeed a delicate child of any age is very prone to show an instability of circulation and heart action and easily induced heart murmurs from fatigue overexertion or mild infection that do not signify the presence of heart disease or active rheumatism which we are so prone to suspect in our climate in New England and rightly so of course in many cases We need more enlightenment in this problem

I have already referred to pregnancy as a factor which alters the height of the diaphragm and so affects both x ray picture of the heart and electrocardiogram but it has other results too Through the influence of the increased blood volume and circulation the heart volume is itself somewhat increased and pulmonary and even apical and aortic systolic murmurs may appear due in part to such factors and in part to the upward displacement of the heart and great vessels

Still further factors significantly affecting the action of the normal heart are the emotions as pointed out by the ancients and restated by Williams Not only may fear and pain alter heart rate blood pressure heart sounds and subjective sensations but through action on the sympathetic and parasympathetic nerves they may even alter the electrocardiogram With tachycardia the *T* waves are often depressed and on occasion excessively so even inversion of the *T* waves has been induced by sudden fright as it has been also but doubtless through a different mechanism by drinking ice water

And finally we come to the toxic influences of drugs or poisons on the normal heart Those that are best known are the effects of digitalis atropine and quinidine but there are doubtless less well known drug actions or the influence of rare poisons that need exploration This is an important digres-

sion for toxic effects on an otherwise normal heart may simulate serious disease as was so well borne out in the famous insurance racket in New York City some years ago when a few crooked doctors lawyers and insurance clients conspired to defraud the companies by the production of ill health and electrocardiographic changes by large amounts of digitalis these symptoms and signs being attributed to coronary disease I myself have taken experimentally, moderate to large doses of digitalis and have not only altered my electrocardiogram with lengthening of *P R* intervals and depression of *S T* segments and *T* waves and induced anorexia and nausea but also caused disagreeably forceful heart action at an ordinary rate as well as extrasystoles and paroxysms of tachycardia Atropine while producing tachycardia lowers the *T* waves of the electrocardiogram as well as does the inhalation of tobacco smoke epinephrine (adrenaline) lowers and may even invert the *T* waves in Lead 2

In later chapters I shall take up in some detail the actual measurements anatomic and physiologic that are considered to be within the range of the *normal heart blood vessels, and circulation and shall also in later chapters* discuss symptoms and signs that may be the result of either cardiovascular diseases or of other factors not related to such diseases There still tends to be *overdiagnosis of heart disease by the erroneous application of both subjective and objective data* I have spent almost as much time in correcting wrong diagnosis of heart disease based on normal variations as I have in *establishing or confirming the presence of actual heart disease One of the most common of all errors* is that of including a large triangle of fat at the cardiac apex as a part of the heart shadow in roentgenologic cardiac mensuration (Figure 7)

In concluding this chapter I have still another observation to make closely related to the present subject and fundamental It may well be the most important thing I shall have presented in this book It is doubtless often a subject of thought but there has been surprisingly little reference to it especially as it relates to the heart Can we tell when an organ is strictly normal? After all what is normal? The word comes from the Latin norma which means rule pattern or carpenter s square Normal health is supposed to be a state of the body in which disease is not discoverable May there not be a few grams of increase in heart weight from one strain or another without lack of ease or objective evidence resulting? May there not be quite extensive change in the coronary arteries of many of us even with narrowing and perhaps small or gradual symptomless occlusions here and there with no lack of ease and with perfectly normal electrocardiograms? And we may have to be run over at ninety or die of pneumonia which proves resistant to chemotherapy Are these coronary changes even if they do produce electrocardiographic abnormalities in old age to be regarded as disease or may they not be considered like gray hairs as a part of the natural process of growing old? When does natural aging stop and disease begin? I find incidentally a great help in using this conception in talking to patients who are going through an acute or chronic

process of adjustment of their coronary circulation with coronary insufficiency so often a temporary state lasting but a few weeks or months or a year or two It is a comfort for the patient to realize that there is not actually a 100 per cent difference between his coronary arteries and those of his friend who feels perfectly well there may be only 3 or 4 per cent He himself may be just over the threshold of clinical evidence and his friend just under

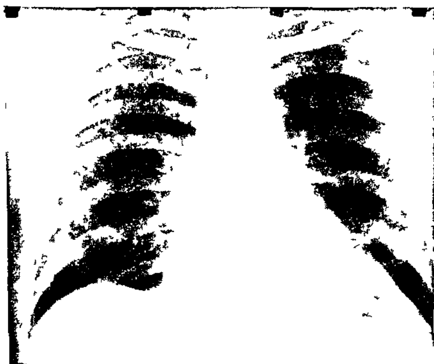


FIG 7 Roentgenogram of healthy fat man showing a large triangle of epicardial fat at the pericardiodiaphragmatic angle on the left a common source of error in estimation of heart size

In summary then let me repeat that we need much more study of normal controls than we possess at present of the heart in all types of mankind and by all methods of examination especially x ray analysis and electrocardiography In the past we have all rushed to what has seemed more interesting and exciting namely the evidence of diseased states so that actually at the present time we are likely to be more thrilled by separating from the category of manifestations of disease certain normal findings than we are to discover disease itself We have put the cart before the horse but it is not too late to change about In the study of pulse rate and blood pressure range we do now have normal standards based on hundreds of thousands of individuals but there is still some uncertainty as to interpretation of borderline readings especially of those in the upper range how high for example may blood pres

sure readings, both systolic and diastolic rise in a normal person from nervousness alone? We need many thousands of normals for x ray heart measurements and electrocardiograms and at the same time better correlations with body build so that we may construct more accurate tables always avoid ing however blind worship of formulas and figures Even statistical analysis helps us but little here for there is still a chance that an individual with measurements at the outer range of normal among thousands of carefully studied cases may himself or herself be either healthy or diseased

Hence until we acquire adequate information and even when we have it we can save ourselves a lot of worry and uncertainty as to whether any given individual has acquired an abnormality of the heart by following Floyer s advice and making a careful routine examination including x ray film and electrocardiogram while the subject is still in excellent health A comparison of serial data on a given person is more valuable than checking him or her against any standard tables

Finally when all is said and done the borderline between the perfectly normal and the slightly but definitely abnormal is so wide not only clinically but anatomically as well that it is unlikely that we can ever draw a sharp line between them nor should we try too hard so to do

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CHAPTER 3

THE PATIENT'S HISTORY AND SYMPTOMS

The present chapter and the next after careful scrutiny as in the case of Chapter 2 have required but minor changes They may I hope continue to be helpful especially to those not already expert in the field of cardiology and to those more experienced who have become careless or hurried in their history taking and physical examinations and who are still too numerous

THE PATIENT'S HISTORY

The diagnosis and treatment of heart disease are dependent upon the history and examination of the patient The capacity to elicit the significant symptoms and signs the ability to analyze these symptoms and signs after they have been found the knowledge of the best therapy and not the least important of all the quick appraisal of the sort of person to be treated are all essential to the satisfactory practice of medicine In one s early days in medicine in school and for a while afterward the analysis of symptoms and signs and to a lesser extent their treatment may be learned with a fair degree of success the ability to elicit the symptoms and signs and the understanding of the individual patient and his reactions are taught less easily by word of mouth or book but come gradually with experience Without this experience in practice one may continue but half trained although able to discourse learnedly on diagnosis and treatment No amount of reading or discussion can take the place of prolonged hard work in the clinic or in the homes of patients the science of medical practice cannot be taught in the classroom

It is therefore impossible for me to do more in this discussion of examination and of symptoms and signs than to point the way and to trust that eventually proficiency may come to each individual who rounds out with his own experience such information as he may find in this and other books Any physician may and doubtless will discover in time innovations or modifications of our present methods of examination and analysis whereby the study and treatment of cardiovascular disease can be furthered Progress in the last generation has been rapid and has been advanced at a fast pace in the last twenty years since the publication of the first edition of this book We have at hand a far better chance to diagnose and to treat heart disease successfully

than had our fathers and there is no reason why this march should not continue With our wealth of methods of examination however there is danger that we may become overconfident or neglectful Sometimes physicians tend to abandon old and tried methods for the new while at other times they shun new and useful methods because they fear they are but transient or because they cannot or do not want to take the time to master them or even to understand them But often diagnosis is so difficult and signs are so misleading that we must make use of all the best tried methods at our disposal before we have properly dealt with a difficult case

In the first part of the book which takes up the examination of patients I shall discuss briefly the methods that have proved valuable and shall have little to say about other methods of less or of doubtful value I shall also discuss the results of these examinations that is the analysis of symptoms and signs, reserving for later parts of the book a detailed consideration of the causes significance and treatment of the cardiovascular conditions revealed by these symptoms and signs

First and most important of all is the story of the patient himself together with a careful consideration of his personality and reactions as he tells his own story If told by someone else especially in the absence of the patient the story has a certain amount of value dependent on the narrator s intelligence and the closeness of his acquaintanceship with the patient but this procedure prevents insight into the case that may come only by listening to the patient s own discussion of his history and symptoms It has been my custom in private practice to allow a full half hour and sometimes longer for the new patient s history except in very simple or special cases I am convinced that this time has been more profitably spent than that of any other part of the examination Not only has it revealed direct information often of great value but it has indirectly revealed knowledge of the type of person recounting his history and most important of all it has almost invariably secured the sympathetic cooperation of the patient Detailed and careful history taking is by no means the general rule It is to be sure, sometimes difficult or impossible in general practice but even when possible it is frequently neglected more I believe in Europe than in the United States Its cultivation is worth serious effort and should not be left to a secretary or assistant It is better to rely on an assistant s physical examination than on his history taking if both cannot be accomplished by oneself I have also found it best for the trained physician to take his own notes of the history during the interview this is preferable to dictation to a secretary or assistant whose presence tends quite naturally to act as a check on free discussion

The patient s history had best begin with a very detailed account of the present illness but under no condition should it be left at that In some cases to be sure it may be necessary temporarily to postpone the rest of the history because of fatigue or serious illness or for another reason but it is essential to remember that significant clues or guides to diagnosis prognosis and treatment may rest in the past history of illnesses operations or accidents in the

opinions or treatment of other doctors (often neglected especially by hospital internes) in the social and occupational history in the account of the patient s habits and last but not least especially from the viewpoint of prognosis, in the family history another frequently neglected source of information

SYMPTOMS

The personal story of the exact onset of the very first heart symptom should be the foundation stone on which the examination of the cardiac patient rests One sentence accurately and adequately presenting this information may be more valuable than all the other data put together An error or vagueness at the beginning may be seriously misleading It is important to remember that not only may cardiac symptoms be confused with noncardiac symptoms but even when cardiac symptoms pain dyspnea and palpitation are actually present they may be confused with each other as in a case of paroxysmal tachycardia wrongly diagnosed angina pectoris or of angina pectoris wrongly labeled breathlessness because of hasty questioning The development of the first symptom its evolution and the appearance of other symptoms must be carefully recorded according to date circumstances character intensity variability and relationship in order to gain full advantage from all available clues

Symptoms are dependent on two primary factors (1) stimulation of sensory nerves and (2) sensitiveness of the nervous system The percentage of responsibility of each factor must be judged in every case it is constantly varying even in the same case at different times Thus a relatively insensitive nervous system may give rise to no symptoms even when there is apparently considerable cause for stimulation while a sensitive nervous system may produce symptoms with very little stimulation If fatigue lowers the threshold of the relatively insensitive nervous system symptoms may be produced by stimulation which before was ineffective if rest raises the threshold of the sensitive nervous system symptoms may no longer be caused by the stimulation heretofore effective

Symptoms do not mean disease they indicate temporary disturbance of function whether or not dependent on structural pathologic changes

I shall consider first the three most important symptoms of cardiovascular origin—pain respiratory disorders and palpitation—and after that a group of less important symptoms

Pain (ποινη penalty) **of cardiovascular origin** In the first place it must be realized that pain in the chest may or may not be caused by trouble with heart or great vessels and that heart trouble may be responsible directly for pain that is outside the chest (referred pain) even when there may be no simultaneous chest pain There are still obscurities about the transmission and interpretation of sensory nerve impulses from the heart but an increasing interest in the autonomic nervous system in the last two decades gives promise of clearing away many of the problems (White J C 1935) It has for example

been demonstrated in recent years that cardiac pain is carried to the central nervous system by the first four or five dorsal rami communicantes on each side by way of the corresponding ganglia from the first (stellate) down and not by way of the cervical sympathetic chains and stellate ganglia alone

Before proceeding to the kinds of heart and great vessel pain, it is important to emphasize that discomfort due to breathlessness or palpitation is not to be called pain although it is true that actual pain may accompany breathlessness or be induced by heart action responsible also for palpitation

Thoracic pain for which heart and great vessels are responsible is best discussed under seven headings (1) precordial aching or heartache, and short sharp stabs of pain (2) substernal oppression either transient (lasting a few minutes) as in the case of paroxysmal angina pectoris or of longer duration (lasting often for hours) as in the case of acute coronary occlusion (3) angina hypercyanotica (4) the pain of acute pericarditis (5) the pain of acute rheumatic carditis (6) pressure pain from aortic aneurysms and (7) the tearing pain of dissecting aneurysms of the aorta Whether pain results from the acute cor pulmonale per se is as yet problematic because of the presence of the underlying acute pulmonary embolism which may itself produce great distress in the anterior thorax or induce coronary pain in a patient who already has considerable coronary artery narrowing or cause pain from the resulting pleuropulmonary infarction An interesting and important cardiac cause of *right upper quadrant abdominal pain* is acute engorgement of the liver with stretching of its capsule secondary to abrupt failure of the right ventricle it may occur paroxysmally on effort (Boyer and White 1942) The most common or important noncardiac causes of substernal or anterior chest pain to be differentiated from the types described above are spasm of esophagus or stomach (cardiospasm) sometimes with hiatus hernia pleurisy muscle and joint discomfort neuritis herpes zoster mediastinal or other intrathoracic tumors pneumothorax and mediastinal emphysema and neurosis

1 *Precordial aching* or *heartache* maximal as a rule in the center of the left breast is the commonest kind of heart pain It may be very mild moderate or very severe and wax and wane for hours to years rarely does it last as short a time as a few minutes on any one occasion When severe it may radiate all over the anterior thorax and even into the arms especially down the left arm in such cases it is easily mistaken for angina pectoris Also when it is severe it is often accompanied by precordial tenderness which is a vitally important clue to the proper interpretation of the heartache itself The essential cause of this kind of pain is oversensitiveness of the nervous system from fatigue or other factor it is characteristic of the majority of cases of neurocirculatory asthenia (see Chapter 22) If it is found in the presence of heart disease itself it is to be interpreted only as a complication and not as a direct result of the heart disease it is however true that the larger the heart and the more forceful its action the more likely are heartache and precordial tenderness to be present The pathogenesis is probably that of the thumping of the heart whether normal or diseased against an oversensitive thoracic wall

Short sharp stabs of pain in the precordium are to be fundamentally explained in the same way as is precordial aching, the immediate cause of such a stab as if from a pin a needle or a knife is in many cases a premature beat or extrasystole

Thus heartache and precordial stabbing sensations are unimportant and in fact often reassuring so far as serious disease is concerned the majority of patients showing such symptoms have no heart disease at all The idea once expressed that myocardial fatigue in chronic heart disease may produce these symptoms has not been borne out in the studies of the last decade or more An interesting observation concerning the *side ache* that not infrequently occurs in either left or right upper quadrant of the abdomen on exertion in normal persons has been presented by Capps (1941) he ascribes this ache to anoxia of the diaphragm on either side

2 *Substernal oppression dependent on coronary insufficiency* is also common but it is of far greater significance than heartache so far as prognosis is concerned It may be mild moderate or severe and may or may not show transmission of pain to arms neck jaws or back Many times heartache of no importance is more severe than angina pectoris of great importance The substernal oppression is almost invariably the result at first of considerable effort under special circumstances such as hurrying for a train on a cold morning in fall or winter directly after breakfast in comparison to the heartache of neurocirculatory asthenia which occurs at any time especially when fatigue sets in at the end of the day Substernal oppression dependent on coronary insufficiency is usually at first paroxysmal lasting but a few minutes at a time as such it has been called angina pectoris (see Chapter 21) When it lasts for hours it is due most commonly to myocardial infarction resulting from acute occlusion of one of the main coronary arteries or branches in almost all cases the result of thrombosis on an atherosclerotic background but in rare cases due to embolism (see Chapter 21) Tenderness over the sternum in cases of substernal oppression does not occur unless there is a complication of neurocirculatory asthenia Actual coronary disease atherosclerotic or otherwise is fundamentally responsible for the large majority of all cases showing substernal oppression dependent on coronary insufficiency in a few cases other factors such as syphilitic aortitis anemia or possibly even coronary spasm itself are wholly or in major part responsible

Sometimes the site of angina pectoris is a little to the left of the sternum (rarely to the right of the sternum) rather than directly substernal very infrequently is it in the middle of the left breast where the more prolonged heartache described above is located and rarely does coronary insufficiency give rise only to referred pain in one or both arms hands or jaws without substernal oppression—in such cases the greatest care and judgment are necessary in its interpretation

3 *Angina hypercyanotica* is rare A heavy pain precordial and substernal with or without radiation is felt by some individuals who have considerable cyanosis especially by a few with marked mitral stenosis or massive pulmonary

embolism and is due probably to myocardial anoxia it has been called angina hypercyanotica

4 *Heart pain of acute pericarditis* is not common The majority of cases of pericarditis acute or chronic have no pain but if there is involvement of certain parts of the parietal pericardium in particular that adjoining the pleura or outer diaphragmatic portion of the pericardial sac there may be disagreeable pain resembling that of pleurisy and usually aggravated by respiration (Capps 1927) the fact that the pain of pericarditis is almost always much increased by the act of inspiration is a very important clue in distinguishing it from the pain of myocardial infarction with which otherwise it may easily be confused The pain originating in the diaphragmatic pericardium tends to be referred to the left shoulder An acute pericardial effusion may cause a vague dull precordial oppression

5 *Heart pain of acute rheumatic carditis* consists of precordial pain sharper than that of the heartache of neurocirculatory asthenia but not so sharp generally as the pain of acute pericarditis although it may complicate the latter It recurs as a rule for a few days during a severe rheumatic infection in childhood It is not a constant finding Its pathogenesis is not clear

6 *Aortic aneurysm pressure pain* is a severe more or less constant ache in upper thorax neck or shoulder dependent on pressure of the growing aneurysmal sac against surrounding tissues especially bones cartilage and nerves it usually requires morphine or alcohol injection of nerves (see Chapter 28)

7 *The pain of a dissecting aortic aneurysm* is usually excruciating and tearing located substernally or in the back and radiating through the chest from back to front or vice versa and often down the back to the legs It tends to be at its height at the very outset in contrast to the pain of coronary occlusion which takes a few minutes to work up to its severest intensity It lasts for hours and usually ends in death due to secondary rupture of the aorta into pleura pericardium, or elsewhere It is due to the extensive tearing of the media of the aortic wall often through its entire length from aortic valve to bifurcation at the common iliac arteries and in large part circumferentially also It is likely to be confused with the pain of acute coronary occlusion (see Chapter 28)

Disorders of respiration There are only three fundamental disorders of respiration that are related to heart disease itself These are (1) dyspnea that is difficult breathing (2) cardiac asthma and (3) periodic apnea and hyperpnea or the so-called Cheyne Stokes respiration Rapid breathing (tachypnea without dyspnea) slow breathing (bradypnea) and sighing respiration are not directly related to heart disease although they are sometimes so misinterpreted particularly the last named Sighing is an important clue when excessive to neurocirculatory asthenia which may or may not complicate heart disease (Figure 8 and Chapter 22)

1 *Dyspnea* (δυσ difficult and πνοη breathing) is of course not pathognomonic of heart disease it has many other causes chiefly pulmonary dis

eases acute and chronic pleurisy with and without effusion bronchial asthma diseases or obstruction of the upper respiratory tract larynx and trachea mediastinal diseases diaphragmatic hernias and certain nervous affections The dyspnea produced by heart disease is mainly the result of a reflex action on the respiratory center from engorgement of the pulmonary circulation Such pulmonary vascular congestion is produced most commonly by failure of the left ventricle and less commonly by the obstruction due to mitral valve deformity (stenosis regurgitation or both) sometimes wrongly interpreted as

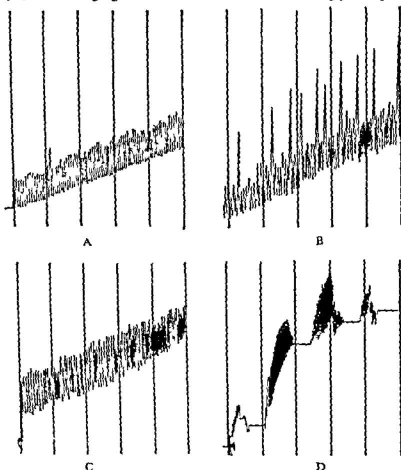


FIG 8 Spirograms showing several types of respiration (*A*) Normal respiration over interval of 5 minutes Inspiration shown by upstroke and expiration by down stroke Respiratory rate = 14 to 16 per minute Time interval 1 minute (*B*) Sighing respiration in case of neurocirculatory asthenia without heart disease Ten sighs are recorded in the interval of 5 minutes Respiratory rate = 12 to 15 (*C*) Dyspnea due to congestive heart failure Note increase in respiratory rate from 14 to 22 toward the end of 5 minutes at which time it was necessary for the patient to change from the supine to the erect position Note the absence of sighing respiration (*D*) Cheyne Stokes respiration The durations of the three hyperpneic phases which are completely shown are 50 55 and 30 seconds respectively and of the three apneic phases 40 35 and 30 seconds respectively

the result of failure of the right ventricle Actual effusion of edema fluid into the pulmonary alveoli in some cases undoubtedly adds its effect in exaggerating the dyspnea probably chiefly through stimulating the respiratory center by the oxygen lack and increased carbon dioxide in the blood Failure *of the right ventricle with resulting stasis and disturbed gas content of the* blood supply to the respiratory center is another cause of cardiac dyspnea but less common and later in appearance Many cases with right ventricular failure constrictive pericarditis or tricuspid stenosis and elevated venous pressure have little or no dyspnea it is probable that such chronic cases accommodate themselves more or less to the high venous pressure increased blood carbon dioxide and decreased blood oxygen in contrast to the dyspneic reaction of acutely congested cases Moreover it is of interest to observe occasionally *the disappearance of dyspnea (due to left ventricular failure)* when the right ventricle fails secondarily and no longer maintains the congestion of the lung vessels

Orthopnea (ορθο erect and πνοη breathing) is the term applied to dyspnea sufficient in degree to force the patient to assume a sitting position such a position acts by gravity to relieve some of the congestion in lungs and brain

2 *Cardiac asthma* (ασθμα gasping) When congestion of the pulmonary circulation occurs suddenly as the result either of acute failure of the left ventricle (see Chapter 30) or of tachycardia in cases of marked mitral stenosis (see Chapter 26) the tension or emphysema (εμ into and φυσημα a blowing sound) that ensues may by nervous reflex action precipitate asthmatic breathing this is cardiac asthma it is not adequately described by any other term such as paroxysmal dyspnea or acute pulmonary edema Of course there is always dyspnea in such cases but asthmatic respiration is a particular type of dyspnea moreover there may or may not be clinically so-called frank pulmonary edema in these cases that is the blood vessels may be greatly engorged with or without interstitial edema but with no actual fluid in the alveoli and bronchioles In fact the squeaking rales of pulmonary emphysema and asthma are much more common in these patients than are moist rales

An attack of cardiac asthma most commonly comes suddenly at night when a patient with chronic heart disease is sound asleep with head and thorax low in position It may infrequently occur on unusual effort when awake The kind of heart disease is that causing severe strain on the left ventricle, especially hypertension aortic stenosis or regurgitation or coronary thrombosis except in rare cases of marked mitral stenosis when tachycardia due to exercise or excitement or occurring paroxysmally suddenly floods the pulmonary circulation

It is important to note that pulmonary congestion or edema may occur acutely or chronically without asthma that asthmatic breathing occurs often without any heart disease at all, but that in an asthmatic type' of individual cardiac asthma is precipitated by acute congestion of the pulmonary circulation it is as Hope pointed out over one hundred years ago (1832), merely bronchial asthma due to bronchiolar spasm added to and set off by heart

failure (see Chapter 30) Cardiac asthma like bronchial asthma is helped though less dramatically by theophylline ethylene diamine (aminophyllin) administered intravenously

3 *Periodic apnea and hyperpnea* (*Cheyne Stokes respiration*) is not pathognomonic of heart disease but it occurs most frequently in chronic cardiac cases with left ventricular weakness combined with an especially poor blood supply to the respiratory center It comes on at first commonly during sleeping hours and tends to begin in very slight degree that is with waxing and waning of respiration but not actually apnea and hyperpnea it is not then such an important sign but its progress should be watched for when it is present during the waking hours it is a serious prognostic sign It is the result of alternating overstimulation of the respiratory center by blood oxygen lack and carbon dioxide excess and overdepression by blood oxygen excess and carbon dioxide decrease It is best treated by stimulation of the respiratory center by theophylline ethylene diamine (aminophyllin) or caffeine along with routine treatment of the myocardial weakness (see Chapter 30)

Palpitation (from the Latin *palpitare* to throb) Palpitation is a much less important heart symptom than pain and dyspnea It consists of an unpleasant sensation of the heart s action whether slow or fast regular or irregular It is usually the result of unimportant disturbance of heart rhythm namely premature beats or extrasystoles and paroxysmal tachycardia (see Chapter 32) or of forceful regular heart action rapid or slow the result of effort excitement toxic effect (for example from tobacco) or infection in a nervously sensitive person Infrequently it may be caused by a more important disorder of heart rhythm such as atrial fibrillation atrial flutter or heart block (see Chapters 33 and 34) In addition to the sensation of palpitation in the thorax there is frequently a sensation of pulse throbbing in the head or extremities more often in the arms than in the legs This is usually regular and forceful and due to effort excitement nervousness fever thyrotoxicosis or reaction to various substances ingested or inhaled for example alcoholic drinks tobacco nitrites It is not per se a sign of heart disease though it is increased in the presence of aortic regurgitation or other cause of a full pulse pressure If present in an observer it may sometimes be difficult to distinguish between his own pulse and the pulse of the subject being examined except by rate

Other symptoms There are several other symptoms frequently occasionally or rarely associated with heart disease but not often directly related Exhaustion nervousness insomnia dizziness headache cough hoarseness hemoptysis faintness syncope anorexia and pain in abdomen or legs are usually but incidental to various complications of heart disease examples are periodic pain in the legs on walking due to arteriosclerosis and faulty blood supply to the muscles (intermittent claudication) and nervousness due to neurocirculatory asthenia Dizziness faintness and even circulatory collapse are sometimes wrongly accredited to heart disease (for example acute coronary occlusion) when actually a severe grade of Meniere s syndrome is present with

faulty function of the internal ear the clue rests in the presence of marked *vertigo* (with nausea as a rule) which is not a symptom of heart disease although mild grades of Meniere s syndrome are frequent accompaniments of hypertension and the degenerative types of heart disease in older persons

Several noncardiac symptoms are at times directly related to heart disease Insomnia may be the result of a poorly defined orthopnea secondary to left ventricular failure and pulmonary vascular congestion Anorexia and upper abdominal pain may be due to engorgement of liver stomach and intestines secondary to right ventricular failure Syncope (with or without convulsions) may be the result of prolonged cerebral anemia secondary to ventricular standstill in heart block of high degree or to extreme tachycardia in paroxysms and rarely a manifestation of angina pectoris a sensitive carotid sinus reflex or a vasovagal reflex of other cause Cough dry in character and sometimes metallic or brassy in quality may result from pressure on air passages or recurrent laryngeal nerve through the presence of aortic aneurysms very large hearts or massive pericardial effusions irritation of pleura or of diaphragm in acute pericarditis may also occasion cough Both cough and hemoptysis may be due to pulmonary vascular congestion in cases of left ventricular failure and of mitral stenosis Hoarseness may appear in rare *cases of aortic aneurysms and mitral stenosis Dysphagia may be caused by* a saccular or dissecting aortic aneurysm anomalous aortic arch dilated left atrium or a large pericardial effusion

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CHAPTER 4

PHYSICAL EXAMINATION

SIGNS WITH ESPECIAL REFERENCE TO CYANOSIS JAUNDICE AND EDEMA

Having obtained the fullest possible information from the patient s own history the physician turns next to the physical examination which fills most of the gaps left in the completion of the picture of the condition of the heart In the writer s experience the relative values of the different parts of the examination are about as follows in percentage of the total history 45 per cent physical examination 25 per cent electrocardiography 15 per cent roentgenology 10 per cent other methods of examination (blood urine basal metabolic rate cardiac catheterization circulation rate vital capacity and functional tests) 5 per cent

There was somewhat of a danger of overemphasis of symptoms and of tests of reserve in the years that followed World War I to the neglect of physical signs This situation was the result of two factors in the first place for ten years or more before that war the pendulum had been set swinging from the extreme point of view of the nineteenth century that structural defects and evidence thereof should be the focus of medical diagnosis prognosis and treatment to the opposite extreme of prime consideration of the functional state of the circulation and secondly the need of manpower for the armed forces during that war forced disregard for ultimate in favor of immediate prognosis The situation was more favorable in this respect so far as the U S A was concerned in World War II

Clues to the etiology of heart disease and to the functional state of the circulation are frequently found in signs other than those presented by the heart directly It is therefore essential in the physical examination of an individual suspected of having trouble with the heart to search the whole body for such clues Hence before taking up the examination of the heart itself I shall present the more important signs of heart trouble elsewhere in the body and discuss in somewhat more detail three special conditions—cyanosis jaundice and edema

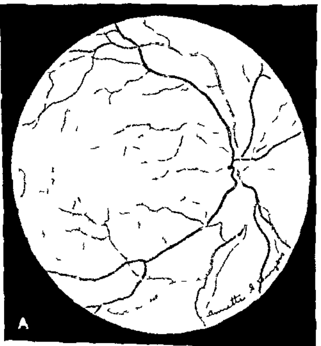
In the first place the general appearance of the patient is of vital importance

this includes age build height and weight (and especially their relationship) nutrition strength mental state color and breathing These various points are often taken in at a glance without careful analysis but they weigh heavily in the final assessment of the case thus affording the physician who personally examines the patient a great advantage over the doctor who is asked to make his diagnosis and prescribe treatment on the basis of hearsay evidence only no matter how careful and detailed may be the history and report of physical signs

Head and neck The eyes afford more clues in a cardiac patient than any other part of the body except the neck and the heart itself Exophthalmos and related eye signs suggest at once the probability that at least some of the heart trouble is due to thyrotoxicosis The failure of the pupils to react to light (Argyll Robertson pupil) and their irregularity and inequality indicate at once the need to search for aortitis itself since central nervous system syphilis and cardiovascular syphilis are frequently associated The arcus senilis is not an important clue however it is only a little more common in older individuals with heart disease than in those without The same statement is true of cataracts The eye grounds on the other hand are of considerable importance especially when there is uncertainty about the degree the duration or even the past existence of high blood pressure important hypertension is attended in the course of a few years by sclerosis of the small arteries of the eye grounds which becomes marked in degree and may be attended by edema exudate hemorrhages and even choking of the disks, when the hypertension becomes malignant (Figure 9) Petechial hemorrhages in the conjunctivae are frequently found in subacute bacterial endocarditis

The mouth and throat should be examined for infection of teeth gums and tonsils which may sometimes lead to acute rheumatic heart disease or to acute or subacute bacterial endocarditis in persons susceptible to these diseases (see Chapters 14 and 15)

The neck may show several important abnormalities Thyroid gland enlargement suggests thyrotoxicosis Vigorous arterial pulsation with the subject at rest is indicative of chronic hypertension aortic regurgitation or aneurysmal dilatation A tracheal tug (sometimes called Oliver s sign Oliver 1878) is uncommon when it is clearly evident it points to the presence of an aortic aneurysm *Increased activity of the carotid sinus reflex determined* by firm pressure exerted by the fingers high up on the carotid artery in the region of the bulb may reveal itself in marked slowing of the heart rate drop in blood pressure or reflex cerebral vasoconstriction with resulting faintness or syncope such a finding may be helpful in explaining symptoms of obscure origin (Weiss and Baker 1933) Finally and most important of all there is engorgement or pulsation of the jugular veins with the subject in the upright position this means most commonly congestive heart failure involving the right ventricle or the whole heart less often it means acute or chronic constrictive pericarditis which blocks the entrance of blood into the heart and least often it indicates organic tricuspid stenosis or regurgitation or obstruc-



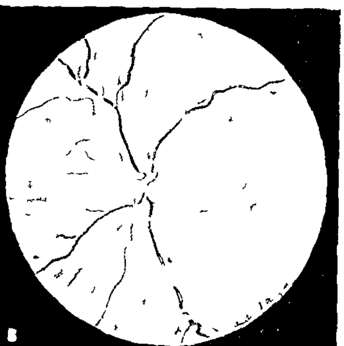


FIG 9 *Photographs of the fundus oculi* (*A*) Right eye of a normal blond man age 23 (*B*) Left eye of a 36 year old blond man with malignant hypertension retinal arteriosclerosis and generalized arteriosclerosis Blood pressure 240 mm mercury systolic *and 142 mm diastolic* *Albuminuria* and granular casts Retinal arteries tortuous irregular in caliber and in various stages of sclerosis Veins are engorged irregularly dilated and markedly compressed by superimposed ar teries The superior temporal vein is bordered by white lines *Light streaks* are increased on the arteries and on the anter ior arches of the veins The relatively normal fovea with its reflex resembles the so-called "hole in the macula owing to surrounding retinal edema Scattered o er the fundus there are two kinds of exu lates one *pale yellowish white solid look* ing the *other* (around macula) small superficial white line powdered snow Radiating from the di k in the mar ner of opaque nerve fibers there are areas of retinal edema stretching into the periphery and n spots obscuring the blood ve els There are many small retinal hemorrhages in various stages of *ab orpt on* Th e wa a n la cond t on n the ght eye (Kindness of Mrs W ll m H W lm B lt mo e)

tion of the superior vena cava by tumor aneurysm or other mediastinal in volvement The deep systolic jugular pulse should not be confused with the carotid pulse (see Chapter 8)

Thorax Chest deformities have two interesting relationships to heart disease Precordial bulging of the bony thorax without other important de formities signifies usually the development of cardiac enlargement due to con genital defects or rheumatic involvement during the period of early growth it is therefore valuable as a sign of important affection of the heart in early childhood Marked scoliosis and kyphosis may themselves give rise to heart disease or more often to insufficiency of the lungs and in rare cases a de pressed sternum may embarrass the heart (see Chapter 23) Abnormal pulsa tions and elevations of the chest wall are found in cases of aortic aneurysm (Figure 10) and of cardiac hypertrophy Palpation of the intercostal spaces



FIG 10 Photograph showing a localized bulging at the right of the upper sternum due to an aneurysm of the ascending aorta and innominate artery

in the dorsal and axillary parts of the thorax may reveal arterial pulsations that indicate the presence of congenital coarctation of the aorta Cardiac pulsations will be discussed in the next chapter

Examination of the lungs is of great importance in heart disease There may be moist rales at the bases due to pulmonary edema resulting from failure of the left ventricle but such rales must be carefully distinguished from atelectatic rales and from rales due to pulmonary infection or multiple infarction distinctions which are frequently neglected Moreover too much has been made of this sign in contrast to that of simple dyspnea or of emphysema with wheezy respiration due to the more common engorgement of the pulmonary circulation in failure of the left ventricle and in mitral stenosis of high degree The emphysema in such cases is primarily a functional state and not usually discoverable at postmortem examination when the lung vessels are emptied it is due to the stiffening of the lung fixation of the alveoli and low position of the diaphragm with the result that relatively little air passes in and out and that only with considerable difficulty Areas of pulmonary consolidation are quite common in heart disease especially infarcts complicating congestive heart failure or mitral stenosis These infarcts are due to embolism from venous thrombosis in abdomen pelvis or legs (most commonly saphenous and femoral venous thrombosis) resulting from the slowed circulation with or without actual phlebitis and are often serious occasionally terminal and frequently overlooked or wrongly labeled pneumonia much less commonly such embolism originates from the right heart chambers Other consolidation of lung tissue may complicate heart disease especially hemorrhagic involvement in severe active rheumatic infection and occasionally a real pneumonic process Finally signs of hydrothorax in a cardiac patient are common the result of an active rheumatic pleuritis or a part of a polyserositis which is usually of unknown etiology or most frequently a transudate due to congestive failure of the right ventricle or whole heart involving especially the right side of the thorax Right hydrothorax is more frequent than left either because of the greater ease of obstruction of the azygos vein on that side or else because of higher venous pressure in the pulmonary circulation of the right lung than in that of the left lung in congestive heart failure (Dock, 1935, White August and Michie 1947) Ewart s sign (Ewart, 1896 Levine and Gevalt, and Gordon 1940), consisting of dullness, increased fremitus and bronchial breathing at the left lung base in cases of pericardial effusion is probably the result of several factors including compression of the lung by fluid in the pleural as well as in the pericardial cavity and pulmonary infarction

Interstitial emphysema of the mediastinum (with or without pneumothorax) is revealed by curious crackling sounds heard over the sternum and sometimes by palpable subcutaneous emphysema in neck or over the anterior thoracic wall (Hamman, 1939 Griffin 1942)

Abdomen There are three signs obtained by examination of the abdomen that are of significance in a cardiac patient The first is enlargement of the liver from engorgement due to congestive failure of the right ventricle to tri

cuspid stenosis or to acute or chronic constrictive pericarditis If the congestion occurs quickly the liver is tender because of the rapid stretching of its capsule Pulsation of the liver that is easily discernible is rare it is the result either of advanced congestive failure of the right ventricle with functional tricuspid regurgitation as in mitral stenosis of long standing or of tricuspid valve disease (rheumatic) of high degree Cirrhosis of the liver may be a coincidental complication of heart disease and failure but in lesser degree it may be a sequel of chronic constrictive pericarditis or mitral stenosis of long standing The second important abdominal sign in heart disease is splenomegaly which is confirmatory of the diagnosis of subacute bacterial endocarditis The third sign is ascites (ασκος bag or bladder) which in a cardiac patient is usually the result of congestive failure of the right ventricle but which may also be caused by tricuspid stenosis or chronic constrictive pericarditis in both of which conditions it more or less parallels the degree of liver engorgement ascites may also be a part of a polyserositis (Concato s disease) which forms the background for chronic constrictive pericarditis (Pick s disease) and it may likewise be caused or aggravated by a complicating cirrhosis of the liver When the possibility of syphilitic aortitis exists inspection of the genitalia for the scar of a chancre may prove helpful

Extremities Abnormal pulses dependent edema cyanosis clubbing of the fingers and toes polyarticular rheumatism and rheumatic nodules are the special signs to be looked for here in a cardiac patient The pulse will be discussed in Chapter 8 Clubbing of fingers and toes associated with cyanosis is found in certain congenital cardiovascular defects (the morbus caeruleus) (see Figure 63 page 298) Clubbing without cyanosis is found in subacute bacterial endocarditis However it must be remembered that clubbed fingers are often found with noncardiac conditions most commonly of all in pulmonary diseases even ulcerative colitis may be the underlying cause and a familial type of unknown etiology has been described Recently it has been found that in all varieties of simple clubbing except hereditary the blood flows per unit surface or volume of finger tip are abnormally high as the result of reduction of the brachial-digital blood pressure gradients this increase of blood flow is probably the important factor in the development of the clubbing (Mendlowitz 1941)

Rheumatic nodules are important evidence of an active rheumatic infection but must be differentiated from the nodes of rheumatoid arthritis (see Figure 84 page 367) It is well also to palpate the dorsalis pedis and posterior tibial arterial pulses if they are much diminished or absent we have evidence as a rule of arteriosclerosis of high degree which may not be limited to the legs or in rare cases of congenital coarctation or of dissecting aneurysm of the aorta Finally absence of the knee jerks suggests the need of searching carefully for syphilitic aortitis while their exaggeration points to the presence of a hypersensitive nervous system which may accentuate cardiac symptoms As a rule the more lively both knee jerks the less serious are the symptoms

There are three particular signs in a cardiac patient that deserve considera tion at some length they are cyanosis jaundice and edema

Cyanosis Cyanosis (κύανος dark blue color) of skin and mucous mem branes is a sign much sought for but unless the cyanosis is well marked or constant it may be unimportant since it often results from temporary local disturbances of the circulation and not from serious disease of heart lun s or blood vessels This change in color is the result of the presence in dilated superficial blood vessels of venous blood in which an abnormally high per centage of the hemoglobin has lost its oxygen (reduced hemoglobin) Two factors are of much importance in determining the degree of cyanosis first the extent of oxygen dissociation or reduction of hemoglobin and second, the degree of dilatation of the blood vessels (arterioles and capillaries) of the skin and mucous membranes which makes the cyanosis visibl The less the oxygen saturation of the hemoglobin and the more dilated the superficial vessels the greater is the degree of cyanosis in any part of the body Arterial blood should normally be 95 to 100 per cent saturated with oxygen which is equivalent to 19 to 20 volumes per cent (the normal oxygen content of at mospheric air) if it is but 80 to 85 per cent saturated so that it contains 3 or 4 volumes per cent of reduced hemoglobin cyanosis results The capillary blood should normally contain about 3 5 volumes per cent of reduced hemoglobin if it contains over 6 5 volumes per cent there results a cyanotic color like that of venous blood which normally contains about 6 volumes per cent of reduced hemoglobin As a rule cyanosis is most common and best seen in lips cheeks ears and hands where the blood vessels are numerous and most exposed to the air This condition is sometimes called *acrocyanosis* (ἄκρος outermost and κύανος cyanosis) A further factor in the production of cyanosis is the amount of hemoglobin in the blood with an increased amount as in poly cythemia the blood possesses a much more pronounced blueness of color due to the high total content of reduced hemoglobin than when there is dilu tion as in anemia even though the percentage of reduction of the hemo globin is the same

The underlying causes of cyanosis are seven

1 The first and most common factor is local and consists of the slowing of the peripheral circulation by cold or vasomotor nervous stimulation Arteri olar vasoconstriction reduces the capillary blood pressure and speed of flow This slowed circulation of the blood allows a greater dissociation of oxygen than usual hence the cyanosis If the cold becomes intense however the dis sociation of oxygen stops and even though the circulation remains very slow the skin color is red and not blue due to the presence of arterial blood An abnormally high degree of sensitiveness to cold especially in the hands with the paroxysmal production of cyanosis (or pallor) is seen in the condition called Raynaud s disease (see Chapter 31) The high degree of circulatory dis turbance in this condition is usually attended by pain Probably both cold and vasomotor nervous stimulation act together in Raynaud s disease

2 Obstruction to the return of blood to the heart may also cause cyanosis either from internal cause namely congestive failure of the right ventricle tricuspid stenosis or acute or chronic constrictive pericarditis or from local causes namely pressure on the veins by tumor or constriction venous thrombosis or incompetent venous valves The slowing of the blood flow through the vessels of the skin causes increased dissociation of oxygen and a blue color exaggerated by capillary dilatation

3 A third very important factor is congestion of the lungs due to heart trouble A chronic engorgement of the lung vessels in mitral stenosis or acute or chronic engorgement from failure of the left ventricle causes a certain amount of blood to pass through the lungs in the middle of the dilated capillaries and so out of contact with the alveolar air continuing into the systemic circulation as venous or blue blood with a considerable dissociation of oxygen If enough of the blood one third it has been estimated is so shunted from venous system to arterial system cyanosis will result Often combined with this factor of engorgement of the lung vessels is that of slowing of the return of blood to the heart from various causes Thus one factor may reinforce another in the production of cyanosis

4 Certain congenital heart defects may cause cyanosis by shunting venous blood directly into the systemic circulation via a single ventricle or dextroposed aorta overriding both ventricles or in transposition of the great vessels or less commonly and later in life through interventricular or interatrial septal defects or patent ductus arteriosus It has been calculated that 30 to 40 per cent of the venous blood must be so shunted in order to assure the presence of cyanosis In patients of this type the capillaries of the skin have been found dilated and the peripheral circulation slowed and it has been suggested that this local factor may be more important in the production of cyanosis than the congenital heart disease itself It is likely however that the veno arterial shunt alone is responsible for most of the cyanosis which is in turn deepened or perhaps even brought to notice by the slowing of the peripheral circulation the slowing of the peripheral circulation is occasioned by the need of the tissues to remove sufficient oxygen from the oxygen deficient blood stream The polycythemia present in most cases of congenital heart disease with a right to left shunt is an additional factor which exaggerates cyanosis Congenital heart defects in which there is no veno arterial shunt are not attended by cyanosis unless there is a complicating factor of congestive heart failure or pulmonary disease

5 Disease of the lungs acute or chronic may be a cause of cyanosis the presence and degree of which are dependent on the amount of pulmonary involvement and on the presence of complicating factors With consolidation of much lung tissue in pneumonia or infarction venous blood in sufficient amount to cause cyanosis is shunted through the pulmonary circulation without coming into contact with alveolar air Moisture in the alveoli and bronchioles may act even more than consolidation to cause cyanosis by preventing contact of blood with air as is the case with severe influenza or

inversely but not in the same degree In nephrosis and starvation edematous fluid is very low in protein giving percentages lower than in any other conditions while the fluid from lymphedema and also from edema in inflammatory areas has a high content of protein the more purulent the inflammatory edema is the higher its protein content and the nearer it approaches the chemical state of blood serum The specific gravity of edematous fluids varies with the protein content from about 1 008 with very little protein to 1 020 or more approaching the specific gravity of blood serum itself Ascitic and hydrothoracic fluids or so called transudates in congestive heart failure have the same composition as subcutaneous edema fluid except for a somewhat higher protein content and a higher specific gravity (about 1 012)

Most of the underlying causes of edema are known In the first place there is the simple effect of gravity Standing long in one position with little or no movement of the legs (contraction of the leg muscles favors an upward flow in the veins) causes a slowing of the circulation with increase in size of the legs from stasis progressing in extreme cases to actual edema which is usually most evident in the ankles just above the shoes and over the shins This edema becomes palpable it is said when the limb volume has increased by 8 per cent The heavier the person and the longer the time on the feet the more likely is the appearance of edema This edema may be regarded as a physiologic occurrence when it is found in heavy persons who stand much of the time Walking or other movement of the feet and legs aids the circulation and tends to prevent edema The presence of varicose veins favors its occurrence especially unilaterally or preponderantly in one leg or the other

Besides gravity a common cause of edema and one of the most frequent is obstruction to the return flow of fluid from tissues to heart Lymphatic block is rarely the cause of any important edema although it may in exceptional cases give rise to chronic massive increase in size of legs or arms or genitalia called elephantiasis Obstruction of the venous circulation is frequently responsible for edema This obstruction may come in a variety of ways (1) by venous thrombosis due to inflammation or to stasis (2) by pressure on veins from without by tumors scars and tight bands and more or less normally late in pregnancy (in the last four weeks) and (3) by resistance to the flow of blood into the heart usually because of the inability of the right ventricle from failure or otherwise to pass on all the blood it receives This venous obstruction also may be due to tricuspid stenosis or to limitation of the size of right heart chambers and venae cavae by a large pericardial effusion or by chronic constrictive pericardial adhesions (as in Pick s disease) so that too small an amount of venous blood enters the heart in diastole with resulting accumulation of edema fluid in tissues and serous cavities The explanation of edema secondary to obstruction of the return flow of blood to the heart from any cause is the increased hydrostatic pressure in the venous ends of the capillaries which results from the increased pressure in the systemic veins and which prevents the normal absorption of fluid from the tissues Krogh Landis and Turner (1932) demonstrated that excessive

fluid accumulates in the tissue spaces in man when the venous pressure (nor mally 6 to 8 cm of water) is raised above 15 to 20 cm

Another important type of edema but much less common than that resulting from venous obstruction with or without cardiac cause is that dependent on physiochemical factors which produce a disturbance of the normal osmotic pressure relationship between the fluids in capillaries and tissues Here dis orders of *either liver or kidneys may play an important role with the onset* of a spontaneous diuresis heralding a beginning recovery The higher concen tration of substances in particular proteins which diffuse with difficulty through the capillary wall in the blood stream than in the body tissues establishes an osmotic pressure which normally draws fluid from tissues into the blood and so tends to neutralize the hydrostatic pressure so far as the fluid balance on both sides of the capillary walls is concerned Nephritis especially with nephrosis and disturbances of tissue metabolism due to starvation are frequently associated with edema this edema is usually general in distribution affecting face arms and hands and not simply the dependent portions of the body as in congestive heart failure Nephritic edema is due fundamentally to damage to the renal tubules which prevents the concentration of the urine and the reabsorption of albumin the low content of albumin in the capillary blood serum prevents the proper return flow of fluid by osmotic pressure into the blood from the tissues A certain type of nephritis with free loss or leakage of sodium tends like Addison s disease with its faulty sodium metabolism toward dehydration and collapse and not edema

Edema secondary to decreased negative osmotic pressure of the blood may be added to edema due to increased positive hydrostatic capillary pressure in a patient with congestive heart failure and malnutrition this is a point of much importance and explains obscure findings in some cases The excessive ingestion of sodium chloride particularly in cases of low myocardial reserve also favors the accumulation of edema in the body tissues

Another important cause of edema in congestive heart failure seems to be due to deficient circulation to the kidneys secondary to failure of the myocardium of the left ventricle or of the whole heart and resulting in inability of the kidneys to excrete sodium normally the retention of sodium results in the building up of the body water both in and out of the circulation

Recently Sarnoff (personal communication 1951) has found that in ex perimental animals excessive stimulation of the vasomotor center in the brain can result in such peripheral vasoconstriction that blood is rapidly transferred in bulk from the systemic circulation to the pulmonary circulation re sulting in pulmonary edema this is probably an explanation for the so-called neurogenic or cerebral type of pulmonary edema

The metabolic disorder of hypothyroidism (myxedema) is commonly associated with a nonpitting accumulation of fluid in the body tissues generally (not primarily in dependent parts of the body) and is attended by a low blood plasma volume in contrast to cardiac edema thyroid therapy clears this myxedema

Beriberi (avitaminosis) is attended by the accumulation of fluid in body tissues but rarely by frank edema

A rare type of edema of unknown cause is hereditary in nature (Milroy 1892 Braham and Howells, 1948)

There are two other varieties of edema that need little comment here because of their ease of recognition and their absence of connection with cardiovascular disease (1) local tissue edema associated with an infectious or toxic process the commonest kind of edema of all and (2) angioneurotic edema (Quincke 1882) also generally localized

Edema due to heart disease may be of any degree from slight edema of the lungs or over ankles or shins developing after a considerable length of time in the standing position to massive edema (called *anasarca* ἀνά upon or throughout and σάρξ flesh) of much of the body in extreme cases even affecting the arms chest wall and face With extensive cardiac edema fluid tends to accumulate also in the peritoneal cavity (ascites) pleural cavities (hydrothorax) especially the right where it appears earlier than in the left and even in the pericardium (hydropericardium) Edema of one side of the body (as of face arm chest abdominal wall or leg) may sometimes be more marked than that of the other side it may be found that this is the effect of gravity the patient having been lying on that side of the body When however in an ambulatory patient edema is confined to one leg or is much more marked in one leg than in the other local venous obstruction (or vasodilatation) is the probable cause Cardiac edema may be associated with some other type of edema in the same case

Edema of the brain is the result of infection hemorrhage infarction or toxic influences such as alcoholism its occurrence in heart disease is not clearly recognized even when there is extensive anasarca involving the upper part of the body in the course of extensive congestive heart failure Edema of lungs may be found in noncardiac patients as the result of infection infarction nephritis or toxic state or as an unusual reflex to pleural trauma or to central nervous system disease when of cardiac origin it results from failure of the left ventricle or from obstruction to the entrance of blood into the left ventricle by marked stenosis of the mitral valve It is to be noted that pulmonary edema is due to left ventricular failure and not to right ventricular failure in fact when right ventricular failure follows failure of the left ventricle as often happens, congestion and edema of the lungs decrease and sometimes disappear entirely Edema of the liver and other abdominal and pelvic viscera is commonly due to failure of the right ventricle or of the whole heart to marked tricuspid stenosis or to acute or chronic constrictive pericarditis Edema of heart and skeletal muscle is not common it has been noted in extensive general anasarca and in beriberi

Finally it is to be noted that bilateral pitting edema of the legs is much less commonly due to heart failure than to other causes especially local venous circulatory fault even in cardiac patients themselves Much digitalis has been wastefully prescribed in such cases before careful appraisal of the heart itself

has demonstrated its futility in these patients of course heart failure may by chance eventually supervene and then digitalis may clear the new increment of edema

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CHAPTER 5

PHYSICAL EXAMINATION OF THE HEART ITSELF

INSPECTION PALPATION PERCUSSION AND AUSCULTATION

This chapter and the next along with Chapters 3 and 4 concern themselves with the simplest and yet the most fruitful methods of examination requiring only the use of the voice the ears the eyes the fingers the stethoscope the blood pressure instrument and especially the intelligence all of which are at once available to the practicing physician Time and effort supply the necessary experience

One is very prone in these days of the machine age to abandon the patient training and skilled use of the unaided senses Nowhere is this truer than in the practice of medicine It has become rather too easy in hospitals or even in the doctor s office to make a roentgen ray examination of the heart and to neglect inspection palpation and percussion But the senses of sight *touch and hearing unaided by instruments except for the simple convenience* of a stethoscope and of a sphygmomanometer are still well worth cultivating When the senses are highly trained and skillfully used they establish such a justified feeling of confidence that it is possible to obtain much information about heart size and shape even when the roentgen ray is not available and also to secure other important data about the heart not shown by the roentgen ray *as in the case of palpable thrills and changes in heart sounds and the* presence of murmurs which reveal much concerning the structural changes in the heart and its functional condition

INSPECTION AND PALPATION

The first important thing to attempt to do on examination of the heart is to locate *the position of the apex* best done with the subject seated and the thorax inclined slightly forward This is possible in the great majority of cases failing only in a few obese or very sick patients Both inspection and palpation aid in this purpose but more especially palpation which by the use of the trained fingers permits the identification of the maximal impulse as the site *of the cardiac apex Such identification is usually in agreement* within a few

millimeters with the position of the apex as determined by orthodiagraphy A measurement of the horizontal distance of the maximal apex impulse from the midsternal line tangentially to the front of the chest is recorded in centimeters and compared to the position of the midclavicular line which is a vertical line dropped from a point halfway between the midsternum and the outer end of the left clavicle as noted below (Figure 11) The position of the cardiac apex should lie in the left fifth intercostal space in or to the

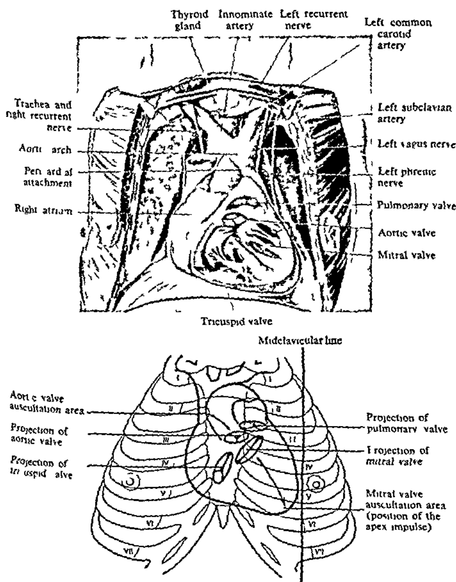


FIG 11 Topographic relationships of the heart and great vessels The heart chambers and blood vessels are shown in a distended state (Corning *Lehrbuch der topographischen Anatomie* 1917)

right of the midclavicular line in a normal adult sitting or standing except in rare instances when the heart may be displaced upward and a little outward from great abdominal distention as in pregnancy The average position of the midclavicular line in the normal adult is 8 to 8½ cm to the left of the midsternum varying from 7 to 10 in the extremes of body size The maximal apex impulse falls normally on this line or ½ to 1 cm within it rarely when the thorax is long and the heart vertical in position so that it is almost centrally placed in the chest the cardiac apex is low often behind the sixth rib or rarely in the sixth intercostal space and as much as 1½ to 2 cm medial to the midclavicular line If it is beyond the midclavicular line in the fifth space enlargement of the heart is to be diagnosed unless the heart is displaced by fluid or air in the right pleural cavity by a depressed sternum or by retraction of the left lung and pleura If the heart is displaced upward appreciably its apex tends to lie in the fourth intercostal space or behind the fifth rib and may then be normally slightly (½ to 1 cm) beyond the midclavicular line In infants and very young children especially when they are fat the apex impulse is normally often in the fourth intercostal space just beyond the midclavicular line

Certain changes of body position and of the height of the diaphragm cause considerable shifting of the position of the apex impulse when the heart is normally freely movable The three greatest shifts are produced as follows (1) a change from the left to the right lateral decubitus causes a shift of the mediastinum and its contents including the heart laterally, the cardiac apex impulse moving often as much as 4 or 5 cm from left to right, from out toward the anterior axillary line to a point not far to the left of the sternum, such a shift does not markedly affect the angle of either the anatomic or the electric axis and so produces little change in the electrocardiogram which in part explains why such a test of change of position is of little value in the diagnosis of adhesive pericarditis (2) A change in the height of the diaphragm produced readily by deep breathing alters appreciably the position of the apex impulse both laterally and vertically from say a point in the midclavicular line underlying the fifth rib to a point 1 to 1½ cm inside the midclavicular line underlying the sixth rib such a shift does markedly affect the angle of both anatomic and electric axes of the heart and so produces usually a striking change in the electrocardiogram particularly in Lead 3 (see Figure 4 page 33) (3) A change from the supine to the standing position alters somewhat the position of the apex impulse partly by straightening out the heart (that is in slight to moderate degree making it more vertical), partly by producing a rotation from left to right and partly by causing a drop of the heart as a whole the result is somewhat like that caused by deep inspiration but not so pronounced and more complicated in mechanism the effect on the electrocardiogram is very variable but usually not marked (see Chapter 9)

Finally it is to be noted that the nipple line is not a suitable guide to heart size chiefly because of its great variation in distance from the midsternum in

individuals of the same size (as much as 2 or 3 cm in extreme cases) but also because as a rule its position is normally 1 to 2 cm beyond the site of the cardiac apex

The major pulsatory movements of the thoracic wall which may be seen and felt resulting from the action of an enlarged heart are often complicated but their analysis may aid in elucidating the heart condition they have been made the subject of a monograph by Dressler (1933 and 1937) A few major points of interest are the rocking movement of the thorax when the left ventricle is very large and forceful the left thoracic wall moving outward and the right inward in systole and vice versa in diastole the forward thrust of the anterior thoracic wall with retraction of both lateral walls in systole when the right ventricle is very large and strong together with a visible and palpable forceful impulse in the region of the pulmonary artery in some such cases when the chest wall is not too thick and an outward thrust of the right chest wall in systole when the atria are markedly enlarged as in the case of the occasional huge left atrium found in advanced mitral valve disease and of the large right atrium in tricuspid valve disease the outthrust being due not to atrial contraction but to the forceful ventricular pulse transmitted directly into the atrium through the incompetent valve These are more or less major pulsatory movements in addition to the apex impulse itself When the heart is much enlarged and its action forceful the fifth and sixth ribs are outwardly displaced at each heart beat

Two other points about cardiac pulsation are worthy of comment First a very active heart whether enlarged or not will produce such a forceful apex impulse that it is widely felt and may be misleading it is the maximal point of this impulse or rather a few millimeters beyond but not its furthest point out that marks the position of the apex itself Second a systolic retraction of the fourth and fifth intercostal spaces just to the left of the sternum often well seen in a person with a thin chest wall is a normal occurrence when the heart is not enlarged or when only the left ventricle is enlarged and it is not to be interpreted as the result of pericardial adhesions it is due to the withdrawal of the right ventricle from the chest wall when it contracts against the left ventricle which in turn contracts away from the region of the sternum but thrusts its apex up against the chest wall further to the left that is in or beyond the midclavicular line depending on the size of the left ventricle

Thrills The next observation to make in physical examination of the heart is to palpate the precordium for thrills which are often difficult to feel with the untrained hand unless they are very marked in degree exercise by increasing heart action and blood flow helps to make thrills that are faint more evident when a thrill is suspected and is not brought out by exercise it probably does not exist Thrills are relatively rare accompanying a few murmurs only especially the aortic systolic murmur of aortic stenosis and the mitral diastolic murmur of mitral stenosis Valvular regurgitation produces thrills in only the rarest cases whether from aortic regurgitation mitral regurgitation or pulmonary regurgitation and then usually when the valve has an odd deformity

such as eversion or rupture of an aortic cusp or a rupture of mitral cusp or of chordae tendineae

A systolic thrill felt over the precordium but best in the second intercostal space just to the right of the sternum (so-called aortic valve area) and transmitted into (but not limited to) the vessels of the neck is due as a rule to aortic or subaortic stenosis rarely to an aortic aneurysm, it is of interest and importance that such a thrill may be felt well also at the cardiac apex A systolic thrill, felt usually in a narrowly localized area in the second intercostal space just to the left of the sternum (so-called pulmonary valve area) means in most instances congenital stenosis of the pulmonary valve or of the infundibulum of the right ventricle rarely patency of the ductus arteriosus or extreme dilatation of the pulmonary artery A systolic thrill also usually very limited in extent felt in the fourth intercostal space just to the left of the sternum indicates as a rule the presence of an interventricular septal defect A diastolic thrill middiastolic or presystolic in time felt in a small area at the cardiac apex and a little toward the midsternum from the apex is characteristic of a high degree of mitral stenosis but is also found in rare cases of marked dilatation of the left ventricle with rapid blood flow (see Chapter 14) A continuous thrill rather rare felt in the second intercostal space just to the left of the sternum is found in a few cases of patency of the ductus arteriosus or to the right in the extremely rare instances of right aortic arch or dextrocardia plus patency of the ductus arteriosus such a thrill is also characteristic of an arteriovenous communication (called aneurysm) anywhere in the body

Finally it should be noted that the search for thrills may be misleading for three important reasons (1) they may not be felt even in the presence of loud and important murmurs as for example in some cases of aortic stenosis (2) they may be suspected when there is actually nothing wrong and (3) they may be felt in almost unique cases where no murmur can be heard due to the inaudibility of vibrations of very low pitch which are nevertheless of importance

PERCUSSION

Before turning to the subject of cardiac auscultation later in this chapter I welcome the opportunity to say a few words about the much neglected and often despised method of cardiac percussion (*percutere* to strike) Percussion of the heart is valuable in the first place because it aids in determining heart size and shape when it is not possible to carry out a roentgen ray study a procedure that continues to be difficult or impossible in the case of quite a few patients Secondly it is of help in occasional cases when the apex impulse is felt with difficulty or not at all And thirdly it serves as a check on the accuracy of reports of roentgen ray measurements Considerable training and experience are necessary before one can properly rely on the accuracy of cardiac percussion but such training and experience are not difficult and

they are well worthwhile The method of percussion matters little that is whether direct (immediate) or indirect (mediate) whether one uses the finger or special instrument as the pleximeter and whether a hard stroke or a gentle stroke is employed (a light stroke is preferable when the chest wall is thin and the heart near to its surface and a heavier stroke when the chest wall is thick or some emphysema of the lungs is present) The main point is to adopt a definite technic and to stick to it until one becomes expert in its use constantly comparing at first the results obtained with the heart measurements by orthodiagram Percussion involves not only the sense of hearing but also that of touch

Auenbrugger Leopold *Inventum Novum Ex Percussione Thoracis Humani* Vienna 1761

From John Forbes English translation 1824

I The thorax of a healthy person sounds when struck

II The sound thus elicited from the healthy chest resembles the stifled sound of a drum covered with a thick woollen cloth or other envelope

III Over the space occupied by the heart the sound loses part of its usual clearness and becomes dull

IV The thorax ought to be struck slowly and gently with the points of the fingers brought close together and at the same time extended

Scholium Robust and fat subjects require a stronger percussion such indeed as to elicit a degree of sound equal to that produced by a slight percussion in a lean subject

X To be able justly to appreciate the value of the various sounds elicited from the chest in cases of disease it is necessary to have learned by experience on many subjects the modifications of sound general or partial produced by the habit of body natural conformation as to the scapulae mammae the heart the capacity of the thorax the degree of fleshiness fatness and so forth

XLVI Signs of Hydropericardium The sound in the cardiac region is now as completely deadened as if the percussion were applied to a fleshy limb

XLVIII When the heart becomes so much distended by blood accumulated in its auricles and ventricles as to be unequal to propel forward its contents it frequently becomes thereby enormously dilated This dilatation has been called Aneurism of the Heart

The pathognomonic sign of this affection is the complete fleshy sound on percussion existing over a considerable space in the region of the heart

In the course of one s palpation and percussion one may elicit an important symptom namely *precordial tenderness* which in the absence of local trauma or lesion of the chest wall itself is useful evidence of a high degree of nervous sensitivity or fatigue as in cases of neurocirculatory asthenia it is found usually in the absence of heart disease (see Chapter 22)

It is well to percuss first the cardiac apex beginning in the left axilla and working toward the sternum One observes a pronounced change of note and resistance when one reaches the apex (usually 7 to 9 cm to the left of the

midsternum in the normal adult) and this point agrees within a centimeter with that of the maximal apex impulse it tends to be a few millimeters further to the left It is to be compared as is the site of the apex impulse with the midclavicular line Next it is best to percuss the left border of the heart in the third and fourth intercostal spaces an increase of heart size toward the left is usually made out readily and here again there is close agreement as a rule between percussion and orthodiagraphic measurements

Percussion dullness in the third intercostal space to the left of the sternum should not normally exceed one half the distance from midsternum to apex (that is not more than 3½ to 4½ cm according to the size of the individual) it often measures less If it does exceed this we have evidence of abnormality in heart size or shape or both It may be too far to the left even when the apex impulse is in the normal position such a finding is usually indicative of mitral stenosis an atrial septal defect or congenital patency of the ductus arteriosus for the measurement records the size of the left atrium near its appendage and of the trunk of the pulmonary artery

The reason why the left border of the heart can be so well percussed in most cases is because it lies close to the anterior chest wall especially in the sitting and standing positions Obesity and pulmonary emphysema and rarely widely transmitted abdominal tympany may interfere with percussion of the heart

We find a very different situation when we try to percuss the great vessels in the first and second intercostal spaces to left and right of the sternum and under the upper sternum itself It is difficult or impossible to outline these structures when they are normal and sometimes even when they are enlarged because of their small size, their distance from the anterior chest wall and their proximity to resonant air passages and lung apices Only when there is a pronounced abnormality as in the case of an aortic aneurysm does one find increased dullness by percussion to the right or left of the upper sternum respectively It is generally convenient to make a record that there is no abnormal dullness in the region of the great vessels except in the infrequent cases where there is such abnormal dullness rather than to attempt to distinguish doubtful percussion borders The same is true of percussion of the right side of the heart in the attempt to outline the position of the border of the right atrium, it is impossible to percuss accurately this heart border because of its distance from the anterior chest wall there being an error of 1 to 1½ cm under the best of circumstances (the right border of the right atrium in the normal adult is usually about 4 cm to the right of the midsternum while the dullness by percussion extends only 2 to 2½ cm to the right just barely beyond the right edge of the sternum) Clearly defined dullness to percussion in the third and fourth intercostal spaces more than a centimeter to the right of the right edge of the sternum almost always means enlargement of the heart in whole or in part or displacement of the heart to the right or a pericardial effusion rarely this may be found normally when the chest wall is very thin As a rule therefore it is convenient to say that there is no ab-

normal dullness to the right of the sternum when such is true rather than to give measurements which are misleading as to actual heart size

Finally we need no longer trouble with the old designations absolute and relative cardiac dullness they serve no useful purpose

AUSCULTATION

Laennec R T H *De l'auscultation mediate* Paris 1819 Brief extracts translated by myself

About three years ago I began the research the result of which I am publishing today

Some physicians have tried to apply their ears to the precordial region in these cases The heart beat perceived thus simultaneously by the senses of hearing and of touch becomes more evident This method is however far from giving the results it would seem to promise I have found it advised nowhere As uncomfortable for the physician as for the patient the method is so disagreeable that it is practically of no use in the hospitals it is hardly to be suggested in the case of most women and in some of them it cannot be employed at all because of the size of the breasts

I was consulted in 1816 by a young woman who presented general symptoms of heart disease and in whose case the application of the hand and percussion gave little information because of her obesity Since the age and the sex of the patient forbade my using the method of examination already described (that is immediate auscultation) I happened to recall a well known acoustic phenomenon if one applies the ear to one end of a beam one hears very distinctly a pin scratch at the other end I thought that I could profit by this physical property in the case of the patient under discussion I took a sheet of paper rolled it up tightly applied one end of this cylinder on the precordial region and placing my ear against the other end I was as surprised as pleased to hear the heart beat in a manner much more clear and distinct that I had ever done by applying the ear immediately to the chest

I use at present a cylinder of wood pierced in its centre by a tube three lines in diameter and divided in the middle by a screw joint in order to make it more portable

Auscultation of the heart (*auscultare* to listen) has become a time worn method of examination and is considered by some to be old fashioned and unworthy of especial attention but it remains today a source of vital information about the heart and it has actually advanced in importance in the last two decades because of the better understanding of its findings Like percussion it demands careful training and long experience for its mastery but the time spent on it is exceedingly worthwhile Because of our present knowledge about heart sounds and murmurs even direct or immediate auscultation may be practiced with far better success than in the days before Laennec introduced the stethoscope for indirect or mediate auscultation in 1819 but the use of the ear directly applied to the chest is clumsy and inconvenient and does not allow the detection of the fine shades of tone and intensity that is

possible by the use of a stethoscope The most useful instrument is binaural with two easily adjustable chest pieces one a bell and the other a flat resonating chamber with diaphragm (Bowles chest piece) which have a somewhat selective action For physicians who are hard of hearing and for amphitheater clinics audion tube amplifiers are now available With earphone connections there is very little distortion of sounds and murmurs this method has proved to be well worthwhile in demonstrations to large groups during the past few years

Auscultation of the heart should be carried out at the cardiac apex (mitral valve area) in the second intercostal space just to the right of the sternum (aortic valve area) in the second intercostal space just to the left of the sternum (pulmonary valve area) at the left of the mid and lower sternum (septal and tricuspid valve areas) and in the left axilla lung bases and neck for transmission of murmurs Both bell and Bowles chest pieces should be used and if there is any possibility of mitral stenosis and the murmur thereof is not heard with the subject in the upright position it should be sought with the subject supine or lying on the left side and after exercise It is also worth while to listen routinely over the thoracic spine in a search for the continuous murmur caused by coarctation of the aorta

An interesting application of the principle of selective binaural timing of sounds and murmurs to ascertain their points of origin and directions of transmission for example from cardiac base toward apex or vice versa has been introduced and perfected by Kerr and his associates (1937) this acoustic principle is similar to the optic recognition of distances and timing by binocular perspective vision The instrument devised for this purpose has been called the symballophone and can be used helpfully provided the hearing is equal in both ears (they should be accurately tested) and provided experience in the use of the symballophone is gained by practice inertia has delayed any general adoption of this innovation

Phonocardiography (also called stethography in the past) the graphic recording of heart sounds and murmurs by electric reproduction using microphone amplifier and galvanometer has gradually reached a good state of development during the past generation and can usefully supplement the personal use of a stethoscope by a trained observer especially in the exact timing of sounds and murmurs in problem cases Two difficulties have yet to be eliminated the first that of the frequent addition of *artifacts* from extraneous sounds or electric currents to the heart sound records and second that of the sometimes inadequate reproduction of certain murmurs especially the fainter diastolic murmurs of low or high pitch However these difficulties have been largely surmounted One additional benefit may eventually accrue through this technical method of study namely extra information about the state of the heart from variations in inaudible vibrations picked up by the apparatus but which have not as yet received adequate clinical analysis Classroom amplification of heart sounds and murmurs by the additional use of a loud speaker needs further perfection

There were published some years ago (Rappaport and Sprague 1941 and 1942) two interesting and valuable papers on the physiologic and physical laws that govern auscultation and their clinical applications with especial reference to phonocardiography their conclusions are worthy of direct quotation Their 1941 paper was summarized as follows

Rappaport Maurice B E E and Sprague Howard B M D Physiologic and Physical Laws that Govern Auscultation and Their Clinical Application *Am Heart J* 1941 XXI 257

"1 Tones of different periods of oscillation or frequency but of similar in tensity affect the human ear to different degrees The audiogram which is a graphic representation of the threshold of audibility is a measurement of the degree to which human hearing varies with respect to the frequency of vibration of the stimulus

"2 The minimum change in intensity of a sound stimulus to which the human ear is capable of responding varies with the general level of the sound as well as with its *frequency In the auscultatory frequency band as the frequency of the* stimulus is lowered a decidedly greater percentage variation in intensity is therefore required to produce the minimum perceptible change

"3 The human ear is a better detector of changes in frequency than of changes in intensity A sound stimulus with a high sensation level requires less of a fre quency variation to produce minimum susceptibility than does a sound stimulus of a lower sensation level Also the ear is somewhat less sensitive to frequency varia tions at the lower end of the auscultatory frequency band than it is to variations in the upper region

4 In the auscultatory frequency band the frequency of a stimulus may be varied rapidly over a considerable portion of an octave without detection by the ear

5 The auditory sensation produced by a complex sound may be decidedly different in character as well as in intensity when the stimulating level is decreased or increased even though no distortion is introduced As a complex sound such as a murmur becomes more intense the low pitched components appear more prominent to the observer

6 When a sound of comparatively high intensity immediately precedes a sound of considerably lower intensity masking of the sound of lower intensity may result.

7 There are many paths along which heart and chest sounds travel in the human body in order to reach the surface As a result a large percentage of the sound energy never reaches the surface because of viscosity elasticity density spreading reflection and refraction losses

8 The entire auscultatory frequency band for heart sounds and murmurs lies below 1 000 cycles per second An estimation of the lower frequency limit of heart sounds and murmur components puts it in the vicinity of 5 to 10 cycles per second although 30 to 40 cycles per second is the lower limit of audibility

9 Acoustic stethoscopes may be classified as either monaural binaural or differential Either the monaural or binaural stethoscope may be employed for general auscultatory purposes whereas the differential stethoscopes are primarily instruments for localizing and comparing sounds

10 The open stethoscopic chest piece or bell when applied to the patient s

chest may be considered as a diaphragm type of chest piece The skin which is bounded by the lip of the bell forms the diaphragm and the fleshy portion under the skin acts as a damping medium

11 The larger the diameter of the open stethoscopic chest piece the better its response to low pitched sounds This is accomplished at the expense of the higher frequency components

12 The greater the pressure with which the open stethoscopic chest piece is applied to the patient s chest the better is the response of the stethoscope to higher frequency components Thus by varying the application pressure *the physician exerts a variable filtering action upon the sounds* because the natural period of the skin diaphragm bounded by the chest piece depends on the application pressure

13 Open stethoscopic chest pieces of various geometrical shapes have been devised to improve the sound accumulating efficiency of the stethoscope A bell with its interior shaped like a parabola has been a favorite Such chest pieces invariably decrease the efficiency of the stethoscope because they increase the *internal volume of the chest piece*

14 The only important consideration when designing an open stethoscopic chest piece is to keep its internal volume at a minimum and have it so shaped that in the case of an obese patient or one with an inelastic chest wall the bell will not fill with flesh to such an extent as to decrease effectively the diameter of the enclosed diaphragm

15 The diaphragm type of chest piece (Bowles type) which is commonly used in auscultation is especially useful in detecting faint high pitched sounds *When it is applied to a patient s chest the principle of operation* of the Bowles chest piece is similar to that of the open bell except that additional attenuation of the lower pitched heart and chest sound components is obtainable with the Bowles chest piece and this prevents masking of the higher pitched components

16 In the Bowles chest piece as in the open type of chest piece the air volume should be made as small as possible in order to obtain maximum efficiency

17 Between 60 and 400 cycles per second which includes most of the ausculta tory region tests show that the binaural method of auscultation through rubber tubes is on an average 20 decibels better than the monaural method with the ear directly applied to the stethoscope A 20 decibel difference is equivalent to a tenfold increase in sound pressure at the ear drum Only between 850 and 1 000 cycles per second is monaural or direct auscultation more efficient than binaural and this range is too high to be practically useful

18 The changes in the efficiency of an acoustic stethoscope which are caused by varying the length of the tubing although they are not given any consideration by stethoscope users produce an effect upon the quality of sounds Tests show that below 100 cycles per second the efficiency is not materially affected by tubing length Between 100 and 1 000 cycles per second tubing length exerts a con siderable effect that is the efficiency decreases with increased tubing length This efficiency loss occurs in the region of the low intensity high pitched diastolic murmurs and every possible increase in efficiency in this region is of utmost value

19 In order to obtain the most efficient tubing dimensions one should make the tubing as short as possible and compromise on the resistance and volume com ponents The compromise may be approached by plotting a graph representing efficiency versus volume effect and another representing efficiency versus fric

tional resistance effect where the two curves intersect is the point of optimum efficiency

20 For general clinical use an electrical amplifying stethoscope must transmit sounds to the observer with a quality and fidelity equal to that of the average acoustic stethoscope A modification of the frequency response characteristic of an electrical stethoscope will definitely alter the quality and character of the sounds

21 An amplifying stethoscope is not primarily an instrument to be used for making sounds many times louder than they can be heard with an acoustic stethoscope The major advantage of the amplifying stethoscope over the acoustic stethoscope is that it enables one to adjust the intensity to the desired level and thus eliminate a number of modifying characteristics peculiar to human hearing which cannot be overcome with the acoustic stethoscope

22 When filters either electrical or acoustic are used with an amplifying stethoscope they should possess frequency response characteristics similar to those of the various open and diaphragm chest pieces

23 For teaching purposes a loud speaker may be used in conjunction with the amplifying stethoscope The over all frequency response of the loud speaker and amplifying stethoscope must be identical with that of the average acoustic stethoscope in order not to modify the quality and character of the sounds

24 In order to maintain an identical and known relationship between sounds as heard and as recorded the recording galvanometer and audiophone must be fed from the same source that is the same electrical pulsations which pass to the audiophone are fed into the galvanometer

The 1942 paper by Rappaport and Sprague was entitled The Graphic Registration of the Normal Heart Sounds *Am Heart J* 1942 XXII 591

1 When a patient is ausculted in the usual stethoscopic manner the observer does not hear the cardiac vibrations as they actually exist at the source because of three major forms of modification namely

a The heart sounds are altered in their transmission from the source to the surface of the chest

b The heart sounds that reach the surface of the chest are additionally modified by the acoustic stethoscope and the type of chest piece employed

c The observer does not perceive the heart sound vibrations as they are transmitted to the ears by the acoustic stethoscope

2 The three major forms of cardiac sound modification are related to auscultation as follows

a The chest transmissional factor must be considered and handled as a variable quantity

b Modification effects that are introduced by acoustic stethoscopes and their chest pieces may be made non variable No attempts at stethoscopic standardization have as yet been made Until such standarizations are accomplished the stethoscopic factor must be considered as a variable quantity in auscultation

c Modification effects that are introduced by average normal hearing may be considered as a constant quantity in auscultation with the condition that personal factors such as auscultatory experience fatigue surrounding noise level and rhythmic concentration ability are omitted

3 The three major forms of cardiac sound modification that are encountered in auscultation may have the following relationships to phonocardiography

a In phonocardiography as in auscultation the chest factor must be considered as a variable quantity

b The modification effects that are introduced by an acoustic stethoscope and its chest pieces in auscultation may be reproduced perfectly by phonocardiography

c The logarithmic type of modification that is introduced in auscultation by average normal hearing may also be reproduced by phonocardiography

4 Phonocardiographic registration may therefore be considered according to the degree of modification introduced namely

a Linear phonocardiography or the registration of the sound vibrations as they exist on the surface of the chest

b Stethoscopic phonocardiography or the registration of the sound vibrations as they are transmitted to the ears by an average acoustic stethoscope

c Logarithmic (human audiographic) phonocardiography or the registration of sound vibrations as they are perceived by a competent observer if the personal factors are omitted

5 Linear stethoscopic and logarithmic phonocardiography are directly related to auscultation Each phonocardiographic method is a representation of a definite stage of sound transmission in auscultation Deviations may be introduced by a phonocardiograph with frequency response characteristics other than linear stethoscopic or logarithmic Such deviations bear no direct relationship to the auscultatory transmission and detection stages Therefore a phonocardiograph with other than linear stethoscopic or logarithmic characteristics must be considered as either an apparatus of poor design or an expression of the designer's personal opinion unless the deviation is based upon a natural constant

6 The linear phonocardiograph is essentially an electrical sphygmograph which possesses several advantageous characteristics not common to the segment capsule or direct optical type of sphygmograph

7 A linear phonocardiogram when registered over the apex is an apex cardiogram or apex beat tracing

8 A chest piece was devised which makes possible simultaneous phonocardiographic registrations over the same precordial area For example this dual chest piece is useful for simultaneously registering the apex beat and the stethoscopic or logarithmic phonocardiogram at the apex Clinically such simultaneous registrations may be useful in differentiating between the third heart sound and the opening snap of the mitral valve when the isometric relaxation phase of the left ventricle is shortened by mitral regurgitation The apex cardiogram is also useful in timing diastolic events as in venous pulse registration In some persons it is rather difficult to record the venous pulse in such cases the apex cardiogram may be registered instead

9 The first heart sound is composed of four components namely

a The first which is caused by residual vibrations of auricular origin

b The second which is produced at the beginning of the isometric contraction phase of the cardiac cycle (closure of the mitral and tricuspid valves)

c The third which is caused by the opening of the semilunar valves

d The fourth which is caused by the acceleration of the blood in the arterial vessels during the maximum ejection phase of ventricular systole

10 The linear phonocardiograph is capable of registering the first and fourth

components of the first heart sound efficiently but is very inefficient in the registration of the second and third components

11 The stethoscopic phonocardiograph registers the first and fourth components of the first heart sound with some attenuation but does not obliterate the vibrations The second and third components are registered distinctly

"12 The logarithmic phonocardiograph obliterates the first and fourth components of the first heart sound of most normal persons and registers the second and third components distinctly

"13 When a normal person is ausculted the observer rarely hears the first and fourth components of the first heart sound the second and third components are well heard Logarithmic hearing (as indicated by logarithmic phonocardiography) is responsible for this auscultatory condition because of the greater relative attenuation of the low frequency first and fourth components than of the higher frequency second and third components Logarithmic attenuation of the first and fourth components is of sufficient magnitude to bring them below the level of human audibility

14 A simultaneous stethoscopic or logarithmic phonocardiogram and venous pulse tracing may serve as a means of differentiating between a prolonged first heart sound and a first heart sound which is followed by a short systolic murmur In the latter instance it extends beyond the c wave peak

15 Our observations indicate that the second normal heart sound may be composed of four components namely

a The first vibrations which represent the beginning of the diastolic fall in pressure with ventricular relaxation

b The second group of vibrations which are caused by the closure of the semilunar valves (termination of ventricular systole)

c The third group which are most likely due to the arterial wall and blood column vibrations An additional possible source of vibration in this phase of the second heart sound may be the natural period vibration of the chest wall which may conceivably be set into oscillation by the second component

d The fourth component is caused by the opening of the mitral and tricuspid valves

16 The logarithmic phonocardiogram almost always totally obliterates the first third and fourth components of the second heart sound vibrations whereas the stethoscopic and linear phonocardiogram may show all four components This indicates that no matter how competent an observer may be he can hear only the second component of the second heart sound of a normal person because his hearing is logarithmic

17 Although the duration of the normal second heart sound is nearly equal to that of the first, auscultation makes the second sound appear shorter This is explained by the fact that normally two components are audible in the first heart sound whereas only one is audible in the second heart sound

"21 For maximum accuracy in all types of phonocardiographic analysis a phonocardiograph capable of registering the heart sounds linearly stethoscopically and logarithmically should be employed

Thus it becomes evident that much of the discussion about phonocardiography in the clinic in the past has been unsound because of the failure to

recognize the important differences between the various types of phonocardiograms mentioned above namely the linear the stethoscopic and the logarithmic which not infrequently have been erroneously compared as if they were the same in detail Despite the importance of their distinction it is possible that many of the vibrations that are inaudible but that can be recorded may in their variations eventually prove to have almost as much clinical significance as the heart sounds and murmurs themselves this is for future studies to determine Figure 12 illustrates two of the three types of phonocardiogram—stethoscopic and logarithmic—in the same case (see below)

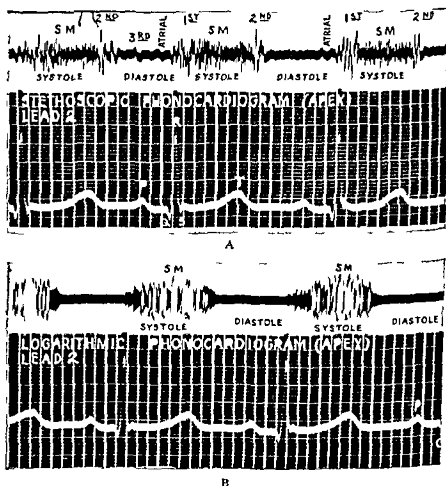


FIG 12 Comparison of stethoscopic and logarithmic phonocardiograms (*A* and *B* respectively) taken at the cardiac apex in the same individual with loud systolic murmur It is of interest to note in the *stethoscopic phonocardiogram the third and the* atrial sounds which are not audible to the human ear and are not shown in the logarithmic phonocardiogram also the difference in the records of the murmur is quite obvious (Kindness of Mr M A Rappaport Sanborn Company Cambridge)

HEART SOUNDS

There are normally three heart sounds but the third is often very faint or even inaudible The first sound loudest at the apex is produced by closure of the mitral and tricuspid valves plus an element of muscular contraction and roughly marks the beginning of systole at its very beginning and merged with it is a very short presystolic phase due to atrial contraction which audible or not is indistinguishable from the first sound itself unless there is abnormal lengthening of the interval between the atrial and ventricular contractions The second sound usually loudest at the base in the pulmonary valve area in children and young adults and in the aortic valve area in the middle aged and elderly is produced by closure of the aortic and pulmonary valves roughly marking the beginning of diastole The third sound in the normal subject heard as a rule best at the apex and thence halfway to the left sternal border when it is audible at all is probably the result of the vibration of the ventricular walls and atrioventricular valve cusps caused by the inrush of blood in every diastole it is best heard in children after exercise and in the recumbent position It occurs early in diastole about 0 1 second after the second sound The opening snap of the atrioventricular (chiefly the mitral) valves if heard at all forms but a late part of the second sound or at most reduplicates it it comes definitely earlier than the time of the third heart sound

The heart sounds are proportionately increased in intensity when the chest wall is thin and as the result of increase in blood flow by exercise excitement or certain drugs They are proportionately decreased by a thick chest wall pulmonary emphysema and a state of weakness prostration or shock

First heart sound The first sound is *accentuated* at the apex when the heart action is forceful and the blood flow is rapid as normally after exercise or excitement and abnormally in thyrotoxicosis and in some cases of neurocirculatory asthenia it is most accentuated in the presence of mitral stenosis with forceful heart action It is not primarily accentuated at the base but it may be so at the lower end of the sternum in very rare cases of tricuspid stenosis

The first sound is *diminished* at the apex and secondarily at the base in the presence of great myocardial weakness and failure and temporarily when there is a state of vasomotor shock approaching then the usually lesser intensity of the second sound at the apex it gives rise to tic tac rhythm Extreme weakness of the first heart sound is a bad sign

The first sound may be *masked* by a systolic murmur either at apex or base The most complete obliteration of this sort is by the harsh systolic murmur of aortic stenosis

The first sound at the apex may be delayed by the hemodynamic conditions that exist in mitral stenosis occurring a perceptible interval after the beginning of the apex impulse itself (Cossio 1943)

Finally the first sound may be *reduplicated* such reduplication is best heard

at the apex and results from either (1) an asynchronism of the closures of the mitral and tricuspid valves, due to asynchronism of left and right ventricular contractions as *in bundle branch block* or to other cause of change in the intraventricular and intra atrial pressure relations or (2) a delay in atrioventricular conduction (first grade of heart block) whereby the atrial contraction sound precedes the first ventricular sound by a small fraction of a second

Second heart sound The second sound is not primarily accentuated or diminished at the apex Its *accentuation* at the aortic valve area with the subject at rest is commonest in cases of systemic hypertension especially *hyperpiesia but it is occasionally louder than normal and metallic in character* when there is dilatation of the aorta in syphilitic aortitis and with marked arteriosclerosis Accentuation of the second sound in the pulmonary valve area may be normally produced by exercise and by deep expiration particularly if *the subject is supine if it is accentuated with the subject at rest* and breathing quietly it is a sign of pulmonary hypertension due most commonly to weakness and failure of the left ventricle occasionally to mitral stenosis and rarely to acute or chronic obstruction in the pulmonary circulation itself (as in the acute and chronic cor pulmonale—see Chapter 20) or to congenital defects especially an atrial septal defect A point of great importance is the relationship between the intensity of the aortic and pulmonary second sounds In an older person and in a patient with systemic hypertension without heart failure the aortic second sound is greater than the pulmonary second sound When in such individuals the sounds become equal in intensity or the pulmonary second sound becomes the louder we have evidence of pulmonary hypertension this in the case of systemic hypertension means weakness and failure of the left ventricle Recovery from the heart failure is attended by a return of the intensity of the pulmonary second sound to a level below that of the aortic second sound

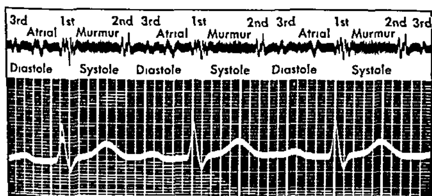
The second sound is primarily *decreased in intensity* to an important degree chiefly at the aortic valve area This is found particularly with aortic stenosis when the sound may be entirely absent and temporarily with a state of vasomotor shock With congenital pulmonary valve stenosis the pulmonary second sound may be much diminished or rarely absent It is to be observed however that the second sound heard at either aortic or pulmonary valve area *may be transmitted to that point from the other side of the sternum* this fact has been inadequately recognized and noted

The second sound may be *masked* by a loud early diastolic murmur at the aortic valve area and along the left border of the sternum in occasional cases of marked aortic regurgitation

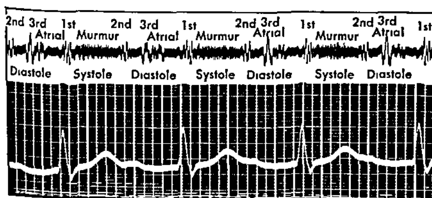
Reduplication of the second heart sound is maximal at the base and is due to asynchronous closure of the aortic and pulmonary valves as the result of a disturbed balance of blood pressure relations between the ventricular cavities on the one hand and the aorta and pulmonary artery on the other hand or of asynchronous contraction of the ventricles as in bundle branch block Re

duplication of the pulmonary second sound is quite common and like the pulmonary systolic murmur may be produced in the normal individual by deep expiration in the supine position When well marked with the subject at rest it is like accentuation of the pulmonary second sound suggestive of mitral stenosis The opening snap of the mitral valve if accentuated may reduplicate the second sound at the cardiac apex

Third heart sound *Accentuation* of the third sound or the appearance of an extra sound early in diastole (Figure 13) may be caused in slight degree by



A



B

FIG 13 Stethoscopic phonocardiograms showing in *A* with normal *P R* interval normal occurrence of first second third and atrial sounds (and a systolic murmur) and in *B* with prolongation of the *P R* interval in the same case the superimposition of third and atrial sounds to give a summation effect (Kindness of Mr M A. Rappaport, Sanborn Company Cambridge)

exercise when marked it is the result of one of three underlying causes (1) most commonly dilatation of either ventricle (2) mitral stenosis or (3) delay in atrioventricular conduction so that the atrial contraction sound falls with it to reinforce it When the third or extra diastolic sound is loud there

is usually a palpable or even visible extra cardiac impulse accompanying it.

Infrequently one hears an extra sound in systole a snap or twang shortly after the first sound and heard best at the cardiac apex It is a curiosity of academic interest only being found as a rule in healthy individuals without heart disease three cases showing this anomaly and diagnosed correctly ante mortem were reported by Huchard (1893) to have had anomalous chordae tendineae that were undoubtedly the cause of the extra sound an instance of interposition of the atrial contraction in the midsystolic phase has also been noted (Hinohara 1941)

Gallop rhythm Gallop rhythm is the descriptive term that has been applied to the auscultatory finding of a well heard extra sound whether in systole or diastole when the heart rate is rather fast, that is 100 or more Its significance is indicated by the factors responsible for the extra sound as outlined above

Gallop rhythm is often hard to time but usually it is easy to distinguish between the systolic and diastolic varieties The former is rare the latter is common In turn *diastolic* gallop rhythm is divided when possible into protodiastolic and presystolic in timing but often it is impossible even with graphic records in the presence of considerable tachycardia to decide which is which and one has then to be content with the simple designation diastolic "

Protodiastolic gallop rhythm that is the kind with the loud third sound early in diastole if it can be so timed when located at the cardiac apex is usually a serious sign since left ventricular dilatation is the commonest accompaniment of marked accentuation of the third sound A protodiastolic gallop rhythm may be heard best at or be limited to the precordium just to the left of the mid or lower sternum in such cases great right ventricular strain is usually very evident and the gallop is probably the result of dilatation of the right ventricle

A *presystolic* gallop is less serious than a protodiastolic gallop it is found when there is slight delay in atrioventricular conduction or in certain cases with very forceful atrial contraction (in chronic hypertension for example)

A *systolic* gallop is of no clinical importance although it may be present in heart disease

In rare cases four heart sounds are heard with each heart cycle the first second, and third sounds and a presystolic sound (produced by atrial systole)

Atrial sounds *Atrial contraction when forceful produces a sound or even* a double sound which ordinarily forms a part of and is buried in the regular first sound of the heart when there is delayed conduction or high grade heart block the atrial sound may be faintly audible at the left border of the sternum or at the apex best heard with the bell and with the subject supine (Figure 14)

There are two other points of special interest about heart sounds that deserve mention One of the curious phenomena in medical observation doubtless dating back to the earliest days of mankind many centuries before auscultation either mediate or immediate is the occasional *audibility of the*

heartbeat at a distance sometimes with the ear but a few inches from the chest wall and sometimes across a wide room One cause of such audibility is left pneumothorax another is pneumopericardium and a third is intracardiac and apparently due to rupture of valve cusp chorda or lax infarcted papillary muscle which allows the mitral valve to slap shut with great suddenness Change of body position and of breathing may greatly affect the degree of audibility

The other point concerns the variation in time interval that may occur even

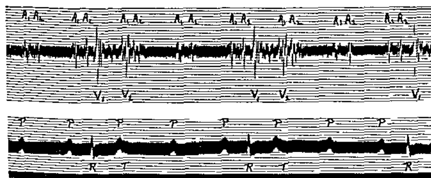


FIG 14 Phonocardiogram (upper tracing) showing double atrial sounds in complete heart block Electrocardiogram taken simultaneously is shown below Time interval = 1/30 second (Lewis *Lectures on the Heart* Kindness of Paul B Hoeber Inc New York)

in successive beats between the electric and acoustic records of the heart s action as has been pointed out in two cases of atrial fibrillation (Luisada 1941) the interval was longer after a short diastole

VASCULAR SOUNDS

In the great vessels at the base of the heart and extending into the neck and below the clavicles sounds may be heard which are transmitted from the heart Over the jugular veins especially over the right sided jugular bulb three sounds may be faintly heard if the pulsation there is vigorous and atrial contraction active These three sounds coincide with the three chief waves normally seen in the jugular pulse the so called *a c* and *v* waves The first is due to atrial contraction and the other two sounds are undoubtedly the result of transmission of the usual first and second sounds from the heart Otherwise the only vascular sound (not murmur) that is audible is that found over any large artery when it is compressed Under certain conditions no compression is needed to hear this arterial sound occurring with the pulse and due to the sudden tension of the arterial wall these conditions are aortic regurgitation and marked peripheral vasodilatation with vigorous heart action both of these conditions being responsible for the relative emptiness of the arteries at the end of diastole when the next pulse comes through Under such

conditions with compression (or even without it) the sound heard over the greater arteries as over the femoral artery at the groin may be very sharp and has been called the *arterial pistol shot sound*

Finally mention may be made of *fetal heart sounds* which undoubtedly were heard with the ear applied to the abdominal wall long before stethoscopes were invented They are usually faint and so rapid that it may be difficult to distinguish between the first and second heart sounds They are generally well heard with the bell receiver attached to the binaural stethoscope *Disturbances of rhythm and rate of temporary significance may be noted* and rarely murmurs or arrhythmia of permanent importance such as congenital heart block may be found Little study has as yet been directed to the possibility of diagnosing heart disease from fetal heart sounds although occasional fetal phonocardiograms have been obtained

CARDIOVASCULAR MURMURS

Cardiovascular murmurs like thrills are produced by the vibration of the valves and walls of the heart and great vessels resulting from the rush of blood from a passage of relatively narrow caliber to one of much greater caliber, and by the vibration of a torn or everted valve cusp or of some tissue floating in the blood stream one end of which tissue is fixed to valve or to heart or vessel wall and quite likely by the effect of certain forceful eddies of the blood in its course through the heart Considering the sinuous course of the blood stream it is surprising that murmurs are not routinely found over all hearts whether normal or not rather than that they occur in only a certain number under basal conditions

Speed of blood flow is the most important modifying factor If the flow is fast the murmur will be louder if the flow is slow the murmur will become fainter and if the flow is very slow the murmur may disappear altogether External modifying factors as in the case of heart sounds are common these include obesity and emphysema which diminish the loudness of the murmurs and leanness which increases their loudness In children murmurs are more easily heard than in adults The transmission of murmurs in direction and extent depends partly on the loudness of the murmur partly on muscular and bony conduction in contrast to the damping action of air fluid and fat and partly on the direction of flow of the responsible blood stream

Certain other observations about murmurs are of importance before discussing the individual types Narrowing of a stream of blood without a fairly abrupt dilatation of the caliber of the containing vessel or chamber further on does not cause murmurs Roughening of the surface of the walls of heart or blood vessels does not cause murmurs unless there are appreciable projections or torn fragments to vibrate in the blood stream It is the relation between the calibers of two adjoining parts of the heart or blood vessels and not the absolute size of the caliber of either that determines the production of murmurs For example there may be a loud systolic murmur in the second inter

costal space close to the sternum if the aorta is dilated even though the aortic valve is normal just as there may be if the aortic valve is stenosed and the aorta of normal caliber Also even though the mitral valve is normal there may be an apical diastolic rumble if well marked dilatation of the left ventricular cavity (with or without aortic regurgitation) is present just as there may be if the mitral valve is stenosed and the left ventricular chamber is of normal size The combination of the two factors in either case that is valvular stenosis and dilatation of aorta or of left ventricular cavity favors an increase in the murmur which may be caused by either factor alone

Heart murmurs may be temporary and due to relatively unimportant functional disturbances It is of great importance to recognize and remember that most systolic murmurs do not indicate the presence of any structural or organic heart disease Nevertheless serious diagnoses and bad prognoses have frequently been made largely on the basis of such murmurs On the other hand it should be recognized that even slight systolic murmurs except in the pulmonary valve area may be abnormal they demand study as to their cause Often they are found to be unimportant functional murmurs but frequently they are evidence of the presence of some important or serious disease acting on the circulatory apparatus even though there be no heart disease itself These facts require the application of study and common sense to the interpretation of murmurs and avoidance of the extreme views with overemphasis and underemphasis which have held sway during the swing of the pendulum in the past generation

At this point I would like to urge a revision of the nomenclature of heart murmurs following suggestions published by Adams Craib and myself (1942) The old time worn phrases functional and organic as applied to murmurs are highly unsatisfactory for important reasons in each case Functional has been used equally to signify physiologic and pathologic and even when its interpretation is the latter there is no separation as to extracardiac or intracardiac causation Organic has been in the past limited to structural deformity of a valve even though there may be present much more serious organic disease of the heart than valvular deformity to cause a murmur which has been labeled functional Also it is often impossible to decide at first at least whether valvular deformity or cardiac dilatation without valvular disease is responsible for a murmur even though it is obviously pathologic Therefore we recommend that the terms functional and organic as applied to murmurs be dropped and the designations physiologic and pathologic used instead with proper subdivision of the latter into extracardiac causation as from anemia and intracardiac causation as from myocardial involvement (rheumatic myocarditis myocardial infarction or myocardial failure) on the one hand and valvular deformity (with stenosis regurgitation or both) on the other There may of course be multiple causes for pathologic murmurs in the same case And in those cases in which we cannot tell whether a murmur is physiologic or pathologic we should so indicate

Furthermore it is of great importance to realize that serious heart disease

(or other diseases) may be present in the absence of all heart murmurs, and even with normal heart sounds in some cases Hypertensive heart disease congenital heart disease the thyroid heart syphilitic aortitis and serious coronary disease with or without angina pectoris may be unattended by heart murmurs. Moreover some conditions while slight in extent give rise to marked murmurs and when greater in degree they become murmurless This may be illustrated by three instances If mitral regurgitation functional or organic is slight in degree with forceful heart action there is likely to be a loud apical systolic murmur due to the small aperture if this mitral regurgitation becomes very extensive with a very large aperture between ventricle and atrium no murmur at all may be found even though the condition is much worse If a congenital defect of the ventricular septum is small as is the rule a loud systolic murmur with thrill characteristic of the condition results but if the defect is so extreme that the *septum is wholly lacking or only rudimentary there is no resultant* murmur at all while the defect is of course far more serious These facts are easily explained by the first comments made above about murmurs A third example is in the case of stenosis of aortic or mitral valve with well marked murmur when heart failure of serious degree sets in this murmur decreases in intensity and may even disappear in rare cases, moreover the presystolic phase of the mitral diastolic murmur disappears when atrial fibrillation replaces normal rhythm

The intensity of heart murmurs may be very simply and adequately expressed by gradation as follows very slight slight moderate loud and very loud This classification may be expressed by the terms *grade 1 grade 2 grade 3 grade 4* and *grade 5* a very useful procedure as advised by Levine *(1933)* In addition to notation of the intensity of heart murmurs there should always be a statement as to their exact timing character (blowing rumbling low or high pitched etc) location and transmission The terms constant" and inconstant have no value as applied to heart murmurs to distinguish between pathologic and physiologic types, since some of the former are inconstant and many of the latter are constant

As is the case with heart sounds so on rare occasions very intense heart murmurs may be heard without a stethoscope and with the ear at some distance from the chest wall even the width of a room Such murmurs either systolic or diastolic in time are in the main very loud and high pitched and are due to unusual valve deformities, especially rupture of cusps or chordae tendineae

Finally it is to be noted that all murmurs heard over the heart are not intracardiac in origin some are due to the movement of air in the lungs as the mechanical result of cardiac contraction or to the rubbing together of pleural or of pericardial surfaces even though uninflamed

Systolic murmurs 1 *At the cardiac apex* (Figure 12 page 80) The systolic murmur heard at the apex of the heart is commonly blowing in character of moderately high pitch but not as a rule musical beginning with or immediately following the first sound and varying from very short in length and slight in intensity so that it is just recognizable as a murmur rather than as an impure

or slurred first sound to a very long and loud murmur filling all of systole The louder this murmur the wider is the area over which it may be heard Transmission of this murmur to a distance is largely based on the two factors of loudness of murmur and nearness of heart to stethoscope as is true in the case of most murmurs An apical systolic murmur therefore which is trans mitted to the left axilla toward the base of the heart or back of the chest is in the main a loud murmur This type of apical systolic murmur is due to systolic regurgitation of blood through the mitral valve from ventricle into atrium This regurgitation may be the result of organic disease (deformity) of the mitral valve usually rheumatic in origin but this is the rarest of the three usual causes It is more commonly due to organic disease of the heart with dilatation without any deformity of the mitral valve But it is most commonly due to some condition elsewhere in the body which acts by causing a temporary or permanent dilatation of the heart without any real organic cardiac disease or mitral valve deformity such a condition may be either physiologic (if temporary) as after exercise in a rapidly growing child or pathologic as in severe anemia When cardiac dilatation is the cause of the mitral regurgi tation and murmur there are two factors to blame the relative importance of which it is difficult to judge The ring of attachment of the mitral valve may be stretched so that the valve no longer fits tightly or the ventricular dilatation by displacing the papillary muscles downward and outward may prevent the chordae tendineae from stretching sufficiently to allow the valve cusps wholly to close Furthermore it is conceivable that some valves which are originally less perfectly constructed leak with very little provocation In the case of a de formed mitral valve it is the shortening and fusion of the chordae tendineae due to inflammation and cicatrization as well as the defects of the cusps themselves that allow the regurgitation of the blood stream

It is not rare for more than one of the three conditions named above causing mitral regurgitation to be present in the same case as for example coronary heart disease with cardiac weakness and dilatation aggravated by severe anemia

Another known cause for an apical systolic murmur besides mitral re gurgitation is transmission of a systolic murmur from the base or from under the lower sternal region such as occurs commonly in cases of aortic stenosis or dilatation and rarely in cases of interventricular septal defect or pulmonary stenosis Such a transmitted murmur heard at the apex but maximal elsewhere is far rarer than a systolic murmur maximal and originating at or near the apex Uncommonly the harsh systolic murmur of aortic stenosis is better heard at the apex than at the aortic valve area itself A point of much value clinically in distinguishing between the systolic murmurs of mitral regurgitation and of aortic stenosis but relatively slightly known or emphasized is that a loud apical systolic murmur due to mitral regurgitation is well heard in the lung bases in the back but poorly at the base of the heart or in the neck while the aortic systolic murmur is poorly heard over the lung bases and well in the neck and at the cardiac apex

Finally a systolic murmur at the apex is in a few cases obviously due to the movement of air in and out of adjacent or overlying lung tissue caused by the mechanical action of the heartbeat itself or to pericardial or pleural rubbing Cardiac systole may compress lung tissue especially if it is fixed over the heart at the apex and squeeze air out or it may cause a suction of air into lung tissue which had been compressed by the heart in diastole It is generally but perhaps not always possible to differentiate this so called respiratory systolic murmur from systolic murmurs of intracardiac origin the respiratory character and particularly it variations in different positions of the body and in different phases of respiration (in one of which especially full inspiration it may disappear entirely) and the relative constancy and quality of the intra cardiac murmur usually distinguish between the two Sometimes rales also are produced in the lungs by the action of the heart causing movement of air back and forth through moisture in the bronchioles this association of rale production with heart action may help to explain respiratory murmurs present in the same case The most common form of cogwheel respiration is respira tion punctuated by frequent respiratory murmurs due to the heart s contraction.

It has been shown that the rubbing together of uninflamed pericardial or pleural surfaces can produce murmurs mostly systolic but sometimes diastolic (Ortiz 1933) Almost certainly some of the extracardiac murmurs heard clinically are of this origin

There may be other causes for the apical systolic murmur which we do not yet know but certain old terms like hemic and accidental should be omitted Anemia malnutrition and infections act by causing cardiac dilatation and speeding up the blood flow and so produce pathologic murmurs of extra cardiac origin

The time intensity and character of an apical systolic murmur and even the presence of a palpable thrill do not show whether or not the valve is damaged though the loudest murmurs masking the first sound and accom panied by thrills are more often found with valvular disease than without it When chronic rheumatic heart disease is present with mitral stenosis the mitral valve lesion may be considered chiefly responsible for the regurgitant murmur and sometimes in young children with a history of recovery from rheumatic fever mitral valve disease may be considered responsible for con stant loud apical systolic murmurs even before mitral diastolic murmurs have developed However is is very important to note that during the acute or subacute rheumatic infection without previous rheumatic attacks both systolic and diastolic murmurs originating at the mitral valve are the result of left ventricular dilatation secondary to the myocardial involvement and not to mitral valve deformity which takes in all probability at least a year and more likely two or three to become established sufficiently to cause murmurs (see Chapters 14 and 26)

A word should be added about the time of the apical systolic murmur As a rule the murmur begins early in systole and continues much of the way through if it fills systole it is sometimes called holosystolic The louder and

harsher the murmur the more likely it is to mask not really to replace the first sound In a few cases it begins at an appreciable interval after the first sound or even in mid or in late systole such a late murmur is more likely to be of respiratory than of intracardiac origin but it may be due to the slow yielding in systole of a weak mitral valve ring

2 *At the base* As in the case of heart sounds there is a distinction between systolic murmurs heard in the second intercostal space just to the right of the sternum and in the same space just to the left of the sternum For the sake of convenience these regions have been called the aortic and pulmonary valve areas respectively and they will be so considered here

(a) *Aortic area* There are four chief causes for systolic murmurs heard at the aortic area They are (1) dilatation of the aorta without aneurysm (2) aortic and subaortic stenosis (3) aortic aneurysm (4) transmission of a systolic murmur from pulmonary area from mid or lower sternum or even from the apex The commonest cause of an aortic systolic murmur is simple dilatation of the aorta whether due to chronic hypertension the dynamic effect of aortic regurgitation arteriosclerosis or syphilitic aortitis Upward pressure on heart and great vessels by high diaphragm as in extreme obesity favors the production of an aortic murmur in such cases hypertension is also frequently present A very important and not infrequent cause of an aortic systolic murmur is aortic stenosis which is most commonly of rheumatic or unknown origin rarely due to congenital subaortic or aortic ring stenosis and in more than slight degree only occasionally the result primarily of calcareous disease although calcification is often superimposed on an already damaged aortic valve to increase the degree of its stenosis in the more chronic cases In the case of congenital subaortic stenosis that is of stenosis of the infundibulum or outflow tract of the left ventricle the loud rough systolic murmur may be better heard in the third right intercostal space or even over the sternum itself than in the second space A murmur transmitted to the aortic area from elsewhere is not rare One of the least common causes of an aortic systolic murmur is a saccular aneurysm usually of the ascending aorta or a dissecting aneurysm of the thoracic aorta

The aortic systolic murmur is generally blowing in character except in aortic stenosis when it is harsh and rough It varies in intensity from slight to very loud the latter intensity usually indicating aortic stenosis in which condition the murmur may be so intense that it is heard all over the chest neck and head and even in rare cases with the naked ear a few inches from the chest wall The aortic systolic murmur tends to be transmitted often in its fullest intensity to the cardiac apex itself along the larger arteries and bones into the neck shoulders arms and back (especially down the spine) and even along the abdominal aorta the louder it is the further it is transmitted With a very loud murmur there is usually a palpable thrill most marked when the murmur is especially rough as is often the case with aortic stenosis The time of onset of the murmur is almost invariably very early and if the murmur is loud and harsh it commonly masks the first sound completely The duration

of the murmur is somewhat variable but usually extends throughout systole and in the case of aortic stenosis it is frequently followed by no second sound at all

(b) *Pulmonary area* A systolic murmur at the pulmonary valve area is often found It is the commonest of all heart murmurs and if it is absent with the subject in the upright position it can usually be brought out in the normal individual as well as in the cardiac patient by the assumption of the supine position especially in full expiration Therefore the pulmonary systolic murmur may be considered to be a normal physiologic event unless of considerable intensity in the upright position even then it should be analyzed carefully before being called abnormal The mechanism of this physiologic murmur is not known but it is probably associated with a dilatation of the pulmonary artery under increased pulmonary pressure as in full expiration (or best in the Valsalva experiment which is an attempted forced expiration with the glottis closed) or with a kinking of the artery by change in position or with *other factors which may lead to dilatation This physiologic pulmonary systolic* murmur is blowing in character begins early in systole but does not mask the first sound extends through most of systole is as a rule not widely transmitted and is associated frequently with accentuation or reduplication of the pulmonary second sound physiologically produced in a similar way

Pathologic dilatation of the pulmonary artery is a much less common but far more important cause of a blowing pulmonary systolic murmur (of varying intensity) than is temporary physiologic dilatation The causes of this pathologic dilatation are (1) pulmonary hypertension most commonly due to failure of the left ventricle but also to mitral stenosis and certain congenital anomalies serious chronic pulmonary fibrosis and emphysema and the rare pulmonary endarteritis (2) thyrotoxicosis which greatly increases the pulmonary blood flow and so dilates the pulmonary artery and (3) rare congenital defects especially an atrial septal defect with resultant flooding of the pulmonary circulation (see Chapter 13) Here as in the case of the physiologic increase of pressure in the pulmonary circulation the pulmonary second sound is often markedly accentuated and may in rare cases be followed by a blowing diastolic murmur which is discussed later in this chapter

Other causes of a pulmonary systolic murmur are rather rare though important Congenital pulmonary stenosis is as a rule but not always accompanied by a loud harsh systolic murmur usually masking the first sound and by a palpable thrill Both murmur and thrill are maximal in the second left interspace near the sternum sometimes a little higher (second rib) and sometimes if the infundibulum of the right ventricle and not the pulmonary valve is stenosed a little lower (third rib or third interspace) Such a difference in site of the maximal murmur and thrill may not however mean a difference in pathologic state The character time relations and intensity of the murmur resemble those of aortic stenosis but the positions differ and the pulmonary stenosis murmur is not so widely transmitted it is sometimes localized to a small area only 2 or 3 cm in diameter but it is usually very well

heard in the lung bases behind Patency of the ductus arteriosus particularly in infants may cause a moderate blowing pulmonary systolic murmur, not so intense as that of pulmonary stenosis and alone not to be interpreted as evidence of such patency A patent ductus arteriosus can be diagnosed by auscultation however only if there is a continuous humming top murmur Aneurysm of the aortic arch or descending aorta may cause rarely a systolic murmur in the pulmonary area as may also the occasional congenital coarctation of the aorta if well marked and the extremely rare true aneurysms of the pulmonary artery itself Finally systolic murmurs from other regions especially from the aortic area may be transmitted to the pulmonary area The fact that the very loud systolic murmurs and pronounced systolic thrills of both aortic stenosis and pulmonary stenosis are sometimes perceived almost equally well on both sides of the sternum or even best over the sternum itself makes the differentiation of these two conditions by auscultation alone at times difficult or even impossible the best differentiation by auscultation is by the transmission of the murmurs that of aortic stenosis being *widely and loudly* transmitted except to the lung bases where it is heard only faintly, and that of pulmonary stenosis being transmitted *not far* except to the lung bases

3 *Elsewhere over the precordium* There are two other areas besides apex and aortic and pulmonary areas where auscultation may reveal maximal sites for systolic murmurs They are at the lower end of the sternum and in the third and fourth intercostal spaces just to the left of the sternum Ruling out in the first place systolic murmurs transmitted from other areas where they are generally much louder we come to the very rare systolic murmurs originating in these two regions To the left of the sternum in the third or fourth intercostal space or in both a loud blowing systolic murmur may be heard in cases of congenital interventricular septal defect If such defect is uncomplicated (as is sometimes not the case) such a murmur is called the Roger murmur (and the condition Roger s disease) A palpable thrill usually accompanies this murmur Pulmonary or more probably infundibular stenosis is a less likely congenital cause for this type and position of murmur Finally a systolic murmur originating under the lower end of the sternum is rare signifying tricuspid regurgitation with a considerable degree of tricuspid stenosis Tricuspid regurgitation which is most often due to dilatation and not to valve damage is in contrast to mitral regurgitation rarely accompanied by murmurs probably because the tricuspid ring is larger and the right heart chamber pressure differences less Mitral regurgitation aortic stenosis or some congenital cardiac defect is by transmission much more likely than is tricuspid disease to cause a loud systolic murmur at the lower end of the sternum

4 *Vascular systolic murmurs* Murmurs systolic in time that is coincident with the appearance of the pulse wave are common over arteries At the base of the heart and in the main branches of the aorta three causes exist for their occurrence marked arterial dilatation with or without saccular aneurysms constriction by internal deformity or pressure from without (with the murmur

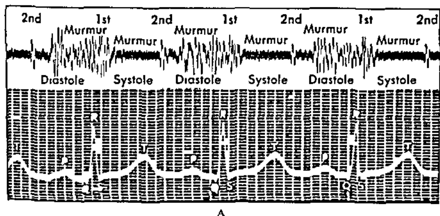
found at the end of the constriction where the caliber increases again to normal or beyond) and transmission of a loud murmur from the aortic area as in aortic stenosis Over the larger peripheral arteries like the brachial femoral, and popliteal pressure applied artificially from without easily produces systolic murmurs and thrills as is observed routinely in blood pressure studies Also compression by tumors cicatrices or other causes may give rise to systolic murmurs and thrills as may large aneurysms with active blood flow Over the veins isolated systolic murmurs are not found but as will later be mentioned continuous murmurs may be present Over the thyroid gland in exophthalmic goiter a very striking vascular murmur is heard called a bruit generally continuous with systolic accentuation and accompanied by a palpable thrill it is doubtless due to the greatly increased arteriovenous blood flow through the hyperactive gland

Systolic murmurs may be heard rather easily with either bell or Bowles type of stethoscopic chest piece but as they rise in pitch they are more readily perceived by the Bowles receiver Certain murmurs are better brought out and are more likely to appear with the subject in one position than in another as for example the pulmonary systolic murmur which may be produced by the assumption of the supine position Finally one systolic murmur may be superimposed on another the harsher or louder one predominating making it very difficult to distinguish the two components

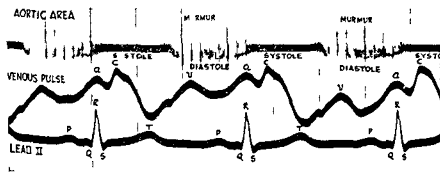
Diastolic murmurs Diastolic murmurs are less common but usually more important than systolic murmurs they have often been called the most serious auscultatory findings but this is not always so since the careful study of heart sounds and the detection and correct interpretation of certain frequent but neglected systolic murmurs may give us more information about the heart in the long run Diastolic murmurs are often difficult to hear It is for their detection that the use of the two stethoscopic chest pieces is so helpful and the examination of the subject in both upright and recumbent positions so important To test the effect of change in position it is most convenient and generally sufficient to examine the patient first upright and then supine or in the left lateral position Before proceeding with the special diastolic murmurs of intracardiac origin it should be noted that in diastole as in systole, though far less often respiratory murmurs may be produced by the action of the heart in squeezing air out of or sucking air into lung tissue especially if the lung happens to be fixed in close contact with the heart Such murmurs can be distinguished almost always by their respiratory quality by the ease with which they are caused to vary or disappear with forced respiration or change in body position by the fact that they tend to occur at an interval after the second heart sound and not directly with it frequently by their nearness to the ear and sometimes by the simultaneous occurrence of pulmonary rales due to the mechanical effect of the heart's action in sucking air in and out through moisture filled bronchioles It is quite likely that a few of these so called respiratory or other extracardiac diastolic murmurs are like systolic

murmurs produced by the friction of uninflamed pericardial or pleural surfaces (Ortiz 1933)

1 *At the apex* The only two diastolic murmurs heard at the apex with any degree of frequency are those due to mitral stenosis and to aortic regurgitation



A



B

FIG 15 *Phonocardiograms showing the diastolic murmurs of mitral stenosis and of aortic regurgitation* (*A*) Stethoscopic electrocardiogram of a classical case of mitral stenosis with very rough mitral diastolic murmur sometimes with presystolic accentuation (note the first beat on the record) Slight systolic murmur also Observe the interval of relative silence between the second sound and the beginning of the middiastolic murmur of mitral stenosis in comparison with the absence of such an interval in the case of the aortic diastolic murmur in (*B*) (*B*) Logarithmic phonocardiogram showing the very musical character of the high pitched aortic diastolic murmur associated with retroversion of an aortic cusp Note that systole is clear Simultaneous venous pulse tracing and Lead 2 of the electrocardiogram are recorded (Kindness of Mr M A Rappaport Sanborn Company Cambridge)

These murmurs unlike superimposed systolic murmurs are so different that even when they occur together they can be differentiated

(a) *Organic mitral stenosis* The murmur of mitral stenosis (Figure 15A) has usually five characteristics that distinguish it from the murmur of aortic regurgitation (1) a rough rumbling character generally of low pitch and

sometimes so low as to be scarcely audible even to a trained ear (2) a failure to appear with or to follow immediately the second heart sound but instead an onset at a definite interval of time after the second sound that time interval being the ordinary interval between the second and third sounds of the heart (3) a localization at the apex often over a small area of but 2 or 3 cm in diameter with no transmission beyond a characteristic that not infrequently causes the murmur to be missed entirely unless the examination is very careful and complete (4) a better perception by the employment of the bell chest piece of the stethoscope than by the employment of other types whose limited use may fail entirely to pick up the murmur when it is not loud and (5) a better perception with the patient recumbent the upright position sometimes failing to reveal the murmur even with the use of the bell receiver To these five characteristics may be added five others found less regularly but which are very useful in distinguishing the murmur (6) a palpable thrill localized closely as a rule over the apex in diastole usually somewhat shorter than the murmur (7) the presence in normal rhythm of a striking accentuation of the murmur in presystole just before or at the beginning of the first sound of the heart and due to the effect of atrial systole but absent if atrial fibrillation is present if the mitral stenosis is relatively slight or if the atrium is empty or weak when it contracts at the end of a prolonged diastole (8) the usual presence of an accentuated first heart sound at the apex so often characteristic of mitral stenosis (9) the common accentuation of the pulmonary second sound and (10) the frequent presence of a loud third heart sound at the left of the lower end of the sternum or in the space between this area and the apex and probably due to dilatation of the right ventricle

The murmur of mitral stenosis is explained by the vibration of heart walls and valve caused by the rush of blood through the stenosed mitral valve into the left ventricular cavity Its greatest intensity is usually at its onset at the time of the third sound when the flow of blood into the ventricle begins (which flow does not occur immediately at the time of the second sound when the aortic valves close at the end of systole) At the onset of the mitral diastolic murmur the flow of blood is as a rule faster than at other times because the intra atrial pressure with left atrium full of blood is greatest at such a time in relation to the low intraventricular pressure which in turn is caused by the passive elastic diastolic ventricular dilatation The force of the blood stream decreases as diastole proceeds and both murmur and thrill tend to fall off in intensity in diminuendo fashion to die away entirely if diastole is long (with atrium almost empty and ventricle full) or if the degree of the mitral stenosis is but slight If normal rhythm exists there is another increase in the speed of blood flow from atrium to ventricle in presystole due to atrial contraction If on account of a short diastole (fast heart rate) or marked valvular stenosis there is still a good deal of blood left in the atrium and still room for more in the ventricle the increase in blood flow through the stenosed mitral valve may be sufficient to cause a final accentuation variable in degree

and sometimes marked of the diastolic murmur and thrill just before the first sound or to make it audible again if it has entirely disappeared

The presystolic accentuation of the mitral diastolic murmur was formerly described as crescendo in character but the crescendo is actually an auditory illusion as shown by phonocardiograms and careful auscultation the illusion is due to the combined presence of a sudden accentuation of a murmur that has largely died away and the sharp first heart sound that terminates it This presystolic part of the murmur of mitral stenosis was at one time considered to be the whole murmur or at least the earliest to appear or the most important or characteristic part. But now we regard it as simply one part of the whole murmur at times striking to be sure but often absent as for example when there is atrial fibrillation (that is no orderly forceful atrial contraction) or too slight a degree of mitral stenosis to produce it If we would rely solely upon the presence of a presystolic murmur for a diagnosis of mitral stenosis we should miss at least half the cases of this valvular lesion Rarely may a pre systolic murmur be present alone without a middiastolic murmur when the force and speed of blood flow through the stenosed valve happen to be greater in presystole than in middiastole and the degree of stenosis not sufficient to cause a murmur at both times Careful study of the case should however be made before recording a diagnosis of mitral stenosis on the basis of what appears to be a presystolic murmur alone without any diastolic rumble or murmur preceding it Marked accentuation and slurring of the first heart sound such as not infrequently occur in an overactive heart may give a sem blance of a slight presystolic murmur and cause an erroneous diagnosis of mitral stenosis to be made when excitement exertion some nervous factor as in neurocirculatory asthenia or thyrotoxicosis is responsible If for any reason there is a suspicion of the possible presence of mitral stenosis because of rheumatic history sharp first sound loud third sound or unusual heart shape size or symptoms and no mitral diastolic murmur is present exercise (or the administration of a nitrite) may be used as a test to increase the rate of the heart and the speed of blood flow and to bring out a typical diastolic rumble at the apex Always it is best to examine the subject recumbent after such a test

Rarely the murmur of mitral stenosis may be a gentle and moderately high pitched blow following the third sound but almost invariably it is rumbling in nature and low pitched when the stenosis is pronounced An apical systolic murmur of mitral regurgitation may or may not be associated with the diastolic murmur of mitral stenosis The louder either one of these murmurs the less intense is the other and if either murmur is marked the other usually is ab sent

Cossio and Berconsky (1943) have pointed out the actual systolic rather than presystolic timing of the very brief vibrations (murmurs) that may pre cede the delayed and accentuated first heart sounds following the shorter diastolic pauses in atrial fibrillation in cases of mitral stenosis

(b) *Functional mitral stenosis* There is another fairly common cause of the mitral diastolic murmur besides actual organic mitral stenosis this is relative mitral stenosis due to considerable dilatation of the left ventricle with the valve normal or not sufficiently damaged to give rise alone to the obstructive diastolic murmur The clinical conditions in which such relative mitral stenosis is found are chiefly three namely moderate to severe acute or subacute rheumatic myocarditis high grades of anemia from any cause and well marked aortic regurgitation In a few scattered cases other causes of left ventricular dilatation are responsible such as congestive heart failure but as a rule cardiac dilatation associated with ordinary congestive failure is not attended by a mitral diastolic murmur in such cases there tends to be a third sound instead Why this is so is not yet clear but it is probably because the blood flow is not fast enough in these hearts

In the case of aortic regurgitation various theories have been expressed as to the pathogenesis of the mitral diastolic murmur It has been generally thought that the blood stream regurgitating through the damaged aortic valve especially if the posterior cusp is involved or through the dilated aortic ostium impinges on the anterior cusp of the mitral valve thus forcing it back and producing a functional stenosis at a time in diastole when the blood stream is pouring from atrium into ventricle another theory suggests the production of the murmur by the contact of the two streams from aortic and mitral valves pouring together into the left ventricle with the anterior cusp of the mitral valve vibrating between them The best explanation however that fits not only the cases of aortic regurgitation but also the cases showing the characteristic murmur with no valve lesion at all is that the left ventricular dilatation is sufficient in degree to give rise to a murmur when the caliber of the blood stream coming through the normal mitral valve suddenly widens out The time relations quality location and other characteristics of this diastolic murmur of functional mitral stenosis are exactly the same as for organic mitral stenosis except that there is as a rule less intensity to it and usually no associated palpable thrill When the mitral diastolic murmur is found with aortic regurgitation without mitral stenosis it has been called the Austin Flint murmur (Flint 1862)

Flint Austin On Cardiac Murmurs *Am J M Sc* 1862 N S XLIV 29

Page 51 As a rule the force of the mitral direct current is not sufficient to develop a murmur unless there be mitral contraction Is this murmur ever produced without any mitral lesions? One would *a priori* suppose the answer to this question to be in the negative Clinical observation however shows that the question is to be answered in the affirmative I have met with two cases in which a well marked mitral direct murmur existed and after death in one of the cases no mitral lesions were found in the other case the lesion was insignificant I will proceed to give an account of these cases and then endeavor to explain the occurrence of the murmur

A mitral direct murmur then may exist without mitral contraction and with

out any mitral lesions provided there be aortic lesions involving considerable aortic regurgitation This murmur by no means accompanies aortic regurgitant lesions as a rule we meet with an aortic regurgitant murmur frequently when not accompanied by the mitral direct murmur The circumstances which may be required to develop functionally the latter murmur in addition to the murmur of aortic regurgitation remain to be ascertained *Probably enlargement of the left ventricle is one condition* [Italics mine]

(c) *Transmitted murmurs* Other diastolic murmurs that may be heard at the apex are transmitted from elsewhere They are due to aortic regurgitation frequently to the very rare pulmonary regurgitation seldom and to tricuspid stenosis probably not at all the murmur in this last named condition not being distinguishable at the apex if it could be heard there from the murmur of mitral stenosis which is almost always much more prominent in such cases

2 *Diastolic murmurs at the base* In the case of basal diastolic murmurs the differentiation of sites is not so important as in the case of basal systolic murmurs since the two diastolic murmurs found are both heard maximally often in the same place and have the same characteristics Other data therefore than site and characteristics must generally be employed to differentiate them the most important point is that the murmur of aortic regurgitation is far more common than that of pulmonary regurgitation

(a) *Aortic regurgitation* (Figure 15B) The auscultatory characteristics that distinguish aortic regurgitation from mitral stenosis and tricuspid stenosis but not from pulmonary regurgitation are (1) a blowing rarely musical quality either high or low pitched often very gentle (2) an onset with or at once after the second heart sound the murmur if intense completely masking the sound (3) a maximal audibility over the midsternum and immediately to the left of it in the third and fourth intercostal spaces usually with wide transmission to the apex and left axilla and upward less loudly toward the neck (4) a better perception with the Bowles type of stethoscopic chest piece than with the bell although rarely certain lower pitched aortic diastolic murmurs may be better heard with the bell or even with the naked ear and (5) a better perception as a rule with the patient upright and leaning forward than recumbent In addition (6) a diastolic thrill is rarely felt accompanying this murmur (7) the murmur continues usually through all or most of diastole decreasing in intensity and never showing a presystolic accentuation (8) the first heart sound is not accentuated in fact frequently both heart sounds are masked by murmurs and (9) an accentuated third heart sound is not usually found Very often particularly if the diastolic murmur is marked there is also an aortic systolic murmur due either to aortic dilatation or to aortic valve stenosis but in the latter case as in mitral valve disease the louder one murmur becomes the less loud is the other that is the greater the stenosis the less the regurgitation and vice versa It is common in aortic syphilis with aortic dilatation and regurgitation for both systolic and diastolic murmurs to be loud all over the cardiac area including the second intercostal space just to the right of the sternum with both heart sounds masked by them

The clinical conditions responsible for the aortic regurgitant diastolic murmur are firstly and much more frequently organic aortic valve disease due to rheumatic infection, syphilitic aortic involvement or sclerotic change a d, secondly dilatation of the aortic valve ostium without disease of the cusps themselves due occasionally to syphilitic aortitis and rarely to chronic hypertension sclerotic change senile ectasia, dissecting aortic aneurysm or severe anemia There is a very interesting variation of the aortic diastolic murmur, more commonly found in syphilitic aortitis than in other conditions consisting of a very loud high pitched musical character with thrill and due apparently to eventration of one of the valve cusps (Bellet et al 1939 Nichols, 1940) (see Figure 15B)

Uncommonly the aortic diastolic murmur is heard better in the aortic area that is in the second interspace just to the right of the sternum than it is along the left sternal border whither it generally is transmitted in maximal degree Such a maximal localization of the murmur in the aortic area is occasionally found in aortic regurgitation associated with marked aortic dilatation due to syphilitic aortitis when the ascending aorta extends further to the right and upward than normally or when along with the aortic valve the ascending aorta is displaced upward and to the right by a very large heart Also rarely the aortic diastolic murmur is heard better at the cardiac apex or at the lower end of sternum or between these sites than along the left border of the sternum if so it can easily be distinguished from the mitral (or tricuspid) diastolic murmur by its other characteristics described above Often the diastolic murmurs of aortic regurgitation and of organic or functional mitral stenosis occur together at the apex and can be readily distinguished Finally it should be stated that the diastolic murmur of aortic regurgitation may be found without any peripheral vascular signs this occurs in the lesser degrees of the valve defect if peripheral vascular signs like the water hammer or capillary pulse are awaited before aortic regurgitation is diagnosed half the cases of this valve lesion will be missed

(b) *Pulmonary regurgitation* Rare but almost exactly similar in its characteristics to the diastolic murmur of aortic regurgitation is that due to regurgitation through the pulmonary valve The resemblance may be so nearly complete that a distinction cannot be made by auscultation alone Rarely however does the pulmonary diastolic murmur ever reach in intensity the loudness frequently found in the case of the aortic diastolic murmur When it is unusually marked it is louder in the second left interspace (pulmonary valve area) than it is in the third and fourth interspaces and follows a much accentuated pulmonary second sound these are important clues In cases with well marked pulmonary diastolic murmurs there may also be other telltale signs namely abnormal visible or palpable pulsation in the pulmonary valve area a loud pulmonary systolic murmur water hammer pulsation in the pulmonary artery and 'dance of the lung hiluses seen by roentgen ray and abnormal right axis deviation by electrocardiogram Usually the pulmonary diastolic murmur is not transmitted so widely as is the aortic With a loud

blowing diastolic murmur along the left sternal border well marked peripheral vascular signs such as the water hammer and capillary pulse are present if the murmur is due to aortic regurgitation and absent if it is due to pulmonary regurgitation this does not apply if the murmur is slight or moderate Percussion and roentgenologic and electrocardiographic studies are especially helpful in the differentiation between aortic and pulmonary regurgitation The clinical conditions underlying pulmonary regurgitation are most commonly (1) mitral stenosis causing increased pressure in the pulmonary circulation and dilatation of the pulmonary artery and valve ring without damage to the valve and rarely the remaining causes (2) chronic failure of the left ventricle with pulmonary vascular congestion and hypertension (3) chronic lung disease giving rise to the same mechanical conditions (4) chronic obliterating pulmonary endarteritis (5) congenital defect of the atrial septum with consequent flooding of the pulmonary circulation (6) congenital defect of the pulmonary valve giving rise to regurgitation (7) perhaps wide patency of the ductus arteriosus and (8) acute or chronic endocarditis of the pulmonary valve itself If mitral stenosis is the underlying clinical cause of the functional pulmonary regurgitation the diastolic murmur resulting is called the Graham Steell murmur (Steell 1881 1888)

Steell Graham *Physical Signs of Cardiac Disease* Edinburgh 1881 2nd ed page 43

Dr Balfour states that a diastolic murmur due to mitral stenosis may be audible and have its maximal intensity in the pulmonary area This murmur is soft and blowing unlike the apex true diastolic murmur of mitral stenosis and is probably produced in the pulmonary artery and infundibulum of the right ventricle as a murmur of high pressure the pulmonary artery being dilated and its valves permitting of a certain amount of regurgitation This murmur is not usually constant at least when first developed (See also *M Chronicle* Manchester December 1888 'The Murmur of High Pressure in the Pulmonary Artery)

3 *Elsewhere over the precordium* the diastolic murmurs heard are those already described transmitted there except for one very rare murmur heard maximally and often solely over the lower end of the sternum This exception is the diastolic murmur of *tricuspid stenosis* In every characteristic except that of position it is similar to the mitral diastolic murmur but it is usually less intense and may have more of a blowing nature In only extremely rare instances is it heard without an equally loud or louder mitral diastolic murmur and since sometimes the latter murmur is transmitted away from the apex and is heard at the lower end of the sternum a diagnosis of tricuspid stenosis by auscultation is rarely justified It may be suscepted if the typical diastolic murmur is louder over the lower end of the sternum than elsewhere over the precordium The presence of a palpable diastolic thrill localized at the same place or much more marked there than at the apex supports the diagnosis of tricuspid stenosis Other signs obtained by roentgen ray and general physical

examination are important The underlying clinical condition is organic tricuspid stenosis due to chronic rheumatic endocarditis

Functional tricuspid stenosis had not been described before I encountered several cases which I believed to be such with well localized mid diastolic murmurs near the lower end of the sternum mitral diastolic murmurs at the apex and loud pulmonary diastolic murmurs autopsy of one of the cases showed mitral stenosis obstructing thrombi in left atrium and pulmonary vessels and marked dilatation of pulmonary artery and right ventricle with no organic disease of pulmonary aortic or tricuspid valves This I reported in the third edition of this book in 1944 and have confirmed since

4 *Vascular diastolic murmurs* Vascular diastolic murmurs are rare Over the great vessels at the base of the heart there may be transmitted for a short distance a diastolic murmur originating in the heart, but this is far less common or marked than in the case of systolic murmurs Otherwise there is only the diastolic murmur produced in cases of aortic regurgitation or marked peripheral vasodilatation by the application of moderate to marked pressure over the larger arteries (best over femoral or brachial artery) First there appears the pistol shot sound and systolic murmur and then as the pressure is increased a slight to moderate blowing diastolic murmur is also heard (not a continuous murmur) The appearance of such a murmur is called Duroziez s sign (Duroziez 1861) The differentiation of the two causes of the murmur has been pointed out by Blumgart and Ernstene (1933) who showed that pressure with the distal and not proximal edge of the auscultatory bell will produce the murmur if aortic regurgitation is the factor responsible while the reverse is true in cases of peripheral vasodilatation in accord with the direction of blood flow and mechanism of murmur production discussed above

Continuous murmurs There is no continuous murmur of cardiac origin but there are three of vascular origin and all three of these may be heard over the region of the heart

1 Probably the most common and certainly the least important cause of such a continuous murmur is the mechanism giving rise to what has been called the *venous hum in the neck* with the subject seated or standing This murmur of humming character is loudest at the right side of the base of the neck and much less loud on the left side It is much increased by bending and turning the head to the left putting the blood vessels on the right side of the neck on the stretch It is easily and quickly obliterated by light pressure on the neck over the jugular veins sufficient to stop temporarily the downward flow of blood or by the assumption of the recumbent position—very simple pathognomonic tests It is a frequent finding in normal individuals especially children It is not evidence of any disease or pathologic state It is probably due to the rapid flow of blood (in the absence of all stasis) through the jugular veins into the jugular bulb and on into the superior vena cava Its importance so far as the heart is concerned is that it is frequently transmitted downward over the base of the heart even close to the lower end of the sternum and may give rise to such erroneous diagnoses as patency of the

ductus arteriosus and even aortic regurgitation if the diastolic phase of the hum happens to be prominent Such mistakes have been made in the past and since many physicians are unaware that there even exists such a phenomenon it behooves all examiners first to know that it does exist and then to exclude it before making a diagnosis of cardiovascular pathologic conditions Lian (1937) has also referred to the probability that rapid blood flow in the superior vena cava may be rarely responsible for a continuous murmur heard along the right sternal border

Brief mention should also be made of the umbilical venous hum heard in some cases of cirrhosis of the liver and in the case of certain congenital venous defects and called the Cruveilhier Baumgarten syndrome (Blain and Clapper 1945)

2 *Patency of the ductus arteriosus* A continuous murmur often with systolic accentuation heard best and sometimes only in the first or second interspace to the left of the sternum a little farther out than the site of the pulmonary systolic murmur and faintly or not at all in the neck is a characteristic sign of patency of the ductus arteriosus If patency of the ductus complicates congenital dextrocardia or a right aortic arch the continuous murmur is heard at the right border of the upper sternum This congenital defect may rarely occur however without murmurs or with but a slight to moderate systolic murmur in infancy or when the patent ductus is of very wide caliber If we can exclude the venous hum in the neck and arteriovenous aneurysms this typical mill wheel humming top machinery or tunnel murmur is pathognomonic of patency of the ductus arteriosus and can usually be confirmed by other findings The murmur may be transmitted to other parts of the precordium though usually it is not and it may be localized so high in the left side of the chest that it is missed on hasty or careless examination Its discovery is generally striking and may occasion undue alarm in the mind of an inexperienced examiner There may or may not be a continuous palpable thrill associated with it there usually is such a thrill if the murmur is intense

A very interesting new continuous murmur is that produced by the surgical treatment of the tetralogy of Fallot (see Chapter 13) here the subclavian (or innominate) pulmonary artery anastomosis produces a patent ductus like murmur on whichever side of the sternum the procedure is carried out

3 *Arteriovenous aneurysm* A continuous murmur usually with some accentuation in systole and attended by a thrill is found on auscultation over any direct arteriovenous connection sometimes called an arteriovenous aneurysm wherever it may be whether in the great vessels at the base of the heart (very rare occurrence) in the lungs in the head or neck or in the extremities (the most common site) Its interpretation is generally easy Such aneurysm is as a rule traumatic in origin by bullet shrapnel knife or even surgical accident (Linton and White 1945) it may be congenital (see Chapter 28)

Appearing abruptly at the left upper border of the sternum in a middle

aged or older individual with syphilitic aortitis a continuous murmur is to be interpreted as the result of rupture of aortic aneurysm into the pulmonary artery a very rare and serious event but one which may be compatible with some weeks or months of survival Correct antemortem diagnosis is possible even though the murmur exactly resembles that of patency of the ductus arteriosus

4 *Arterial aneurysm* A rare cause of a continuous murmur is an arterial aneurysm which may involve the aorta one of its major branches or a peripheral vessel usually over such a lesion if a murmur is heard at all it is only systolic in time but there are conditions such as wide open unthrombosed cavity with rapid blood flow when the murmur continues into diastole

5 *Coarctation of the aorta* Finally in some cases of congenital coarctation of the aorta a continuous murmur of slight to moderate intensity and not continuing throughout all diastole can be well heard over the thoracic spine

PERICARDIAL FRICTION RUB

Finally in cardiac auscultation we should observe the presence or absence of friction sounds due to acute pericarditis Such sounds vary from a soft almost blowing character to extremely rough loud rasping and leathery sounds Usually they are found in both systole and diastole and tend to be somewhat louder in systole They may occur in systole alone which fact adds to the difficulty of their differentiation from systolic murmurs The most common site is near the sternum especially along the left edge but they may be found anywhere or everywhere over the precordium and if loud enough they may be widely transmitted to the back and elsewhere If marked they are attended by palpable thrills It is often difficult in the presence of pericardial friction sounds to recognize the characteristics or even the existence of heart murmurs masked by them and if the friction sounds are of unusually soft character it may sometimes be difficult to distinguish them from murmurs Repeated and daily observations to note the variation and gradual increase or disappearance of such friction sounds may prove necessary for their interpretation and for the diagnosis of underlying valvular or other cardiac disease

Pericardial friction rubs are almost invariably indicative of acute pericarditis but there are occasional exceptions as pointed out by Ortiz (1933) when pericardial friction sounds or murmurs may be produced by normal pericardial surfaces rubbing against each other under unusual pressure particularly in the pulmonary valve area as in cases of pulmonary artery dilatation in thyrotoxicosis (Goodall 1920 Lerman and Means 1933) and of acute cor pulmonale due to pulmonary embolism (McGinn and White 1935)

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SEE ALSO REFERENCES UNDER GENERAL REFERENCES FOLLOWING CHAPTER 2

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CHAPTER 6

SPHYGMOMANOMETRY NORMAL AND ABNORMAL BLOOD PRESSURE

Hales S *Statistical Essays Containing Haemostaticks or an Account of some Hydraulic and Hydrostatical Experiments Made on the Blood and Blood Vessels of Animals* W Innys and R Manby London 1733 Vol 2

Page 1 1 In *December* I caused a Mare to be tied down alive on her Back she was fourteen Hands high and about fourteen Years of Age had a Fistula on her Withers was neither very lean nor yet lusty *Having laid open the left* crural Artery about three Inches from her Belly I inserted into it a brass Pipe whose Bore was one sixth of an Inch in Diameter and to that by means of another brass Pipe which was fitly adapted to it I fixed a glass Tube of nearly the same Diameter which was nine Feet in Length Then untying the Ligature on the Artery the Blood rose in the Tube eight Feet three Inches perpendicular above the Level of the left Ventricle of the heart But it did not attain to its full Height at once rushed up about half way in an Instant and afterwards gradually at each Pulse twelve eight six four two and sometimes one Inch When it was at its full Height it would *rise and fall* at and after each Pulse two three or four Inches and sometimes it would fall twelve or fourteen Inches and have there for a time the same Vibrations up and down at and after each Pulse as it had when it was at its full Height to which it would rise again after forty or fifty Pulses

Hales pioneered in the estimation of venous pressure also On page 13 he wrote as follows

1 In *December* I laid a common Field Gate on the Ground with some Straw upon it on which a white Mare was cast on her right side and in that Posture bound fast to the Gate she was fourteen Hands and three Inches high lean tho not to a great Degree and about ten or twelve years old This and the above mentioned Horse and Mare were to have been killed as being unfit for service

"2 Then laying open the left Jugular Vein I fixed to that part of it which comes from the Head a glass Tube which was four Feet, and two Inches long

"3 The Blood rose in it in three or four Seconds of Time about a Foot, and then was stationary for two or three Seconds then in three or four Seconds more it rose sometimes gradually and sometimes with an unequally accelerated motion

nine Inches more on small Straimngs of the Mare Then upon greater Straimngs it rose about a Yard and would subside five or six Inches

Sphygmomanometry (σφυγμος pulsation μανος thin or rare—rarity or tension—and μετρον measure) consists of measurement of the arterial blood pressure It is a special method of cardiovascular study which through its introduction as a routine part of physical examination during the past generation has revealed the cause of much cardiac enlargement and failure that was previously obscure

Two centuries or more ago and again one hundred years later actual determinations of the blood pressure of animals were made by the insertion of tubes into arteries to measure the height first to which the blood column ascended (Hales 1733) and second to which it forced a mercury column (Poiseuille 1828) but the study was applied only to animals in experimental work until much later However long before the development of a satisfactory clinical sphygmomanometer rough attempts were made to estimate human blood pressure by measuring the weight or force needed when attached to a sphygmograph to obliterate the radial pulse (Vierordt 1855) There followed gradually the methods of pressure application by plethysmograph to the hand (Marey 1876) later by pelottes to the radial artery (von Basch 1881) and then to the brachial artery and finally by small and then larger fluid filled cuffs applied to finger or arm (Riva Rocci 1891) At last came the introduction of the present comfortable wide air filled cuffs for application to the upper arm and to the leg

Arterial blood pressure in man is read off for convenience in millimeters of mercury instead of in centimeters of water (which would require a measuring tube over 13 times longer) The gauge is either a carefully graduated and calibrated tube of mercury or a spring pressure device with dial and needle (von Basch 1887) There are today many different models and makes of sphygmomanometers some of these are more convenient more accurate or better made than others but most of them are satisfactory provided they are checked for accuracy Errors may creep into the use of any type of sphygmomanometer too airtight a seal of a tube containing a mercury column may for example by air compression or by relative vacuum result in errors in blood pressure readings too low during inflation of the cuff and too high during decompression completely to nullify the generally reputed greater accuracy of the mercurial sphygmomanometer A maximal error of 3 mm of mercury may be considered permissible for sphygmomanometers in routine clinical use at pressures up to 300 mm of mercury the average error should be considerably less but great accuracy is not needed clinically since the significance of variations of a few millimeters of blood pressure is generally negligible

Special sphygmomanometers have been devised for special purposes such as the recording sphygmomanometers which take graphic records of value

where objective data are desired for a permanent file and the oscillometer which shows at different pressure levels the fullness of the pulse in a quantitative way The latter is especially useful in studying the peripheral circulation when there is vascular disease or obstruction A useful new instrument introduced to register the blood pressure in the pulmonary artery and its branches the right ventricle the right atrium and the great veins during cardiac catheterization is an electromanometer devised especially for this purpose superseding the Hamilton manometer There are various instruments and methods for the study of the venous blood pressure dependent on (1) the force applied by a pelotte (with manometer) to stop the venous flow (2) the amount of air pressure under a glass capsule measured in centimeters of water necessary to cause collapse of a vein of moderate size usually on the back of the hand or forearm (von Recklinghausen 1906 Hooker and Eyster 1908) (3) the height above the level of the right atrium in centimeters to which the forearm and hand are raised before the veins collapse (Frey 1902 Gaertner 1903) and the most satisfactory method (4) the direct reading of the pressure in centimeters of blood or of sterile normal salt solution in manometer tube connected with a needle introduced into an elbow vein at the level of the right atrium (Moritz and Tabora 1910 Griffith et al 1934 Holt 1940) A method for the graphic registration of the venous blood pressure has also been devised (Kendrew 1926) Finally methods for determining the capillary blood pressure have been introduced including (1) macroscopic blanching of the skin by pressure under a transparent capsule a method which is unsatisfactory because it includes the pressure in the smaller arterioles and venules as well (2) the more accurate microscopic method of direct observation of the blood flow in the capillaries (Lombard 1912) and most accurate of all (3) direct registration of pressure by the introduction of a fine pipette into a capillary (Landis 1930, Eichna and Bordley 1939)

The systemic blood pressure cannot be estimated by palpation alone with enough accuracy to warrant any confidence in such a procedure Instrumental sphygmomanometry is essential There are three technics which as a matter of fact may be combined for the sake of greater accuracy

The best method of clinical sphygmomanometry is the *auscultation* technic which records systolic and diastolic pressures in most cases very slightly below the actual levels as determined by direct readings from within the artery The systolic pressure is to be read at the point when the first clear sound appears during slow decompression of the blood pressure cuff faint sounds due to the impact of a forceful pulsation against the closed end of the artery at the upper edge of the cuff may sometimes be transmitted to the stethoscope placed over the artery at or just below the lower edge of the cuff at any pressure above the systolic but these should be ignored The diastolic pressure should be recorded at the point when the sound abruptly disappears or abruptly drops in intensity rarely the sound continues loudly to zero and the diastolic pressure must be so recorded as in some cases of marked aortic

regurgitation In 1939 a joint report was published by committees appointed by the American Heart Association and by the Cardiac Society of Great Britain and Ireland for the standardization of blood pressure readings in which there appeared a note of difference of opinion relative to a record of the diastolic pressure the American committee recommended that both the level at which the auscultatory sounds become dulled and that at which they disappear (if there is a difference) should be recorded thus 140/80 70 or 140/70 0 or 140/70-70 while the British committee believed that except in aortic regurgitation it is nearly always possible to decide the point at which the change comes (either abrupt dulling or complete disappearance) and that this is the only reading that should be recorded A report by a new committee of the American Heart Association in 1951 states that it appears that the point of complete cessation is the best index of diastolic pressure

There is no practical value in attempting to record the various auscultatory phases of the pulse pressure that is in the interval between the systolic and diastolic levels except in one respect to be recounted below usually the upper most phase is one of sound the second phase which lasts normally over an interval of about 20 or 30 mm of mercury is one of murmur the third phase is one of sound again and occasionally there is a short fourth phase of dimin ished sound before the level of silence is reached below the diastolic pressure The one auscultatory phase that is of special importance and of practical interest is that related to the so called *auscultatory gap* In occasional cases the murmur phase may be largely or wholly absent leaving a gap of absolute or relative silence in the middle or upper part of the pulse pressure range Such a finding is most frequent in chronic hypertension aortic stenosis and marked local arteriosclerosis its exact mechanism is not clear An example of such an auscultatory gap is one of 35 mm ranging from 180 to 145 in a patient with systolic pressure of 210 and diastolic of 105 To avoid an im portant error in such a patient it is necessary to raise the compression of the cuff far enough above this gap so that the true systolic sounds can be heard on decompression or to check the method by either or both of the other two methods of sphygmomanometry one can easily carry out both these pro cedures If the auscultatory gap is not recognized there may be recorded a systolic pressure as much as 50 mm or more below what it actually is There are still other sources of error in auscultatory sphygmomanometry too low a reading when the arm is especially small and too high when the arm is very large but these errors are not great (Bordley and Ragan 1941) and in general the method is an unusually accurate bedside procedure as checked by direct intra arterial readings (Steele 1942)

A second method of sphygmomanometry the *oscillatory* is theoretically more accurate than the other technics but actually less practical because of the frequent difficulty in making the readings The systolic pressure is the point of abrupt increase in amplitude of the oscillations of the mercury column or needle of the manometer above the baseline of small pulse move ments while the diastolic pressure is the first point of distinct decrease below

the maximal oscillations unfortunately however both these points may be poorly marked because of the failure of any abrupt changes The method may be carried out visually or by a recording device (Figure 16) Its greatest value is its service as a check on the accuracy of the more practical auscultatory method except in the study of obstructive arterial disease in the extremities when it has been found that the form of the oscillographic curve is of some importance in determining variations from the normal in the vascular tree and apparently in determining the type of arteriosclerosis (Friedlander 1935)

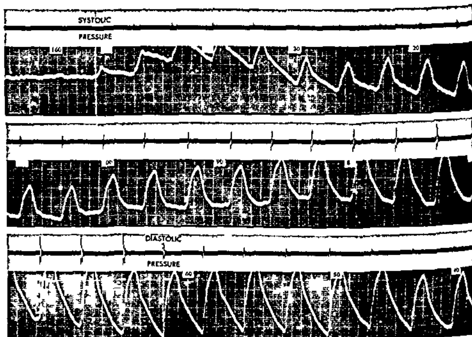


FIG 16 Human arterial blood pressure record determined by simultaneous brachial arterial tracing and phonogram at systolic pressure of 150 and diastolic pressure of 62 The first definite upstroke of the arteriogram occurs just prior to the record of the first sound The disappearance of the truncated dip of the arterial tracing occurs at the time of the last well marked sound record (Kindness of Mr M A Rappaport Sanborn Company Cambridge)

The third method of sphygmomanometry is *palpatory* The point at which the radial pulse is first felt on decompression of the brachial cuff is recorded as the systolic pressure but this is invariably too low by about 5 to 10 mm The method serves however as a rough check on the other methods outlined above The diastolic pressure cannot easily be recorded by palpation and this explains why in the early days of sphygmomanometry only the systolic blood pressure was measured Segall however a decade ago (1940) called attention to the possibility of palpating over the brachial artery the vibrations set up during the pulse pressure interval which correspond to the sounds and murmurs heard by the auscultatory method between systole and diastole

It is of academic interest that the subject himself can roughly note the levels of systolic and diastolic blood pressure in the arm by the sensations during decompression of the cuff a thrill is felt subjectively just below the systolic pressure level and disappears just above the diastolic level

Finally there has been a revival for certain special studies of the old time direct arterial blood pressure by arterial puncture in man (Wolf and Kindler 1934) and there have been introduced in recent years methods of recording by cardiac catheterization the actual pressures in right atrium right ventricle and pulmonary artery and its branches an especially important development (Cournand et al 1944 Dexter et al 1947)

Systemic arterial blood pressure The blood pressure in the brachial artery of a normal adult ranges from 95 to 145 mm of mercury *systolic* depending on conditions at the time of the sphygmomanometry Age has some effect on blood pressure as recently confirmed by Master (1950) There tends to be an increase though often irregular in systolic pressure of ½ to 1 mm a year Thus at twenty years the systolic blood pressure normally may be 110 mm at thirty in the same person 115 at sixty 150 and so on Factors of excitement exercise eating smoking and fatigue all play a considerable role in many persons tending to elevate the systolic blood pressure moderately Nervous tension is the factor that influences blood pressure most elevating it in both normal and hypertensive individuals but especially in the latter Ayman and Goldshine (1940) found for example that in a series of hypertensive individuals 30 per cent registered a systolic pressure 40 mm or more higher in the clinic than at home and 24 per cent a diastolic pressure 20 mm or more higher The temporary hypertension that is found in many nervous but otherwise normal young men at the time of examination for athletic sports military service or insurance is well known in fact it is so common that routine blood pressure determination for admission to the army was at one time even considered inadvisable Figure 17 illustrates the wide range of the normal brachial blood pressure

The pressure varies also slightly with the respiratory phase but this is unimportant unless the respiration is greatly disturbed or the heart constricted by acute or chronic pericarditis when the pulse may become markedly *paradoxical* (see Chapter 27) the paradoxical pulse consists of marked decrease of the systolic and pulse pressures even to the point of obliteration during inspiration in contrast to the usual and normal increase of the pulse during inspiration in the case of diaphragmatic breathing

In the early morning before arising the systolic brachial arterial pressure may be 105 mm while in the same person in the midst of a busy day it may register as much as 140 strenuous exercise may send it up to nearly 200

The most important and commonest cause of abnormal high systolic blood pressure is hyperpiesia (essential or arterial hypertension) less common causes are nephritis obstruction to the renal circulation (Goldblatt 1934) convulsive seizures brain tumor tumor of the adrenal medulla (pheochromocytoma) and coarctation of the aorta (see Chapter 19) The causes of ab

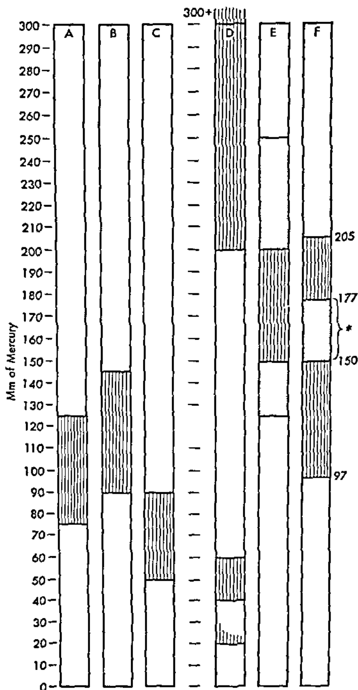


FIG 17 Diagram showing (*A*) the average normal adult blood pressure (1?5 mm mercury systolic and 75 diastolic) (*B*) the usual upper limits of normal pressure (*C*) the lower limits of normal pressure (*D*) the extreme upper range of pressure with hypertension and an extreme lower range of pressure with hypotension the diastolic pressure in aortic regurgitation may drop almost to 0 (broken lines) (*E*) the variability of the systolic pressure (from 250 to 200) and of the diastolic pressure (from 150 to 125) possible over an interval of 10 minutes in a given case of hyperpiesia

normally low systolic blood pressure are vasomotor or vascular shock Addison s disease and to a lesser degree acute and chronic constrictive peri carditis and aortic stenosis

The *diastolic* arterial blood pressure range is normally much less than the systolic a low reading in an adult is 60 mm of mercury and a high 90 It re cords the basic pressure in the circulatory system and so is fundamentally more important than the systolic pressure which is but very transient at its full height

The causes of abnormal increase of the diastolic blood pressure are the same as those recorded above for the systolic pressure The causes of ab normal decrease of the diastolic pressure are the same as for decrease of systolic pressure and in addition aortic regurgitation

In late years particularly in France much interest has been expressed in the so-called *average dynamic* or *mean effective* blood pressure which is the total pressure leveled off from the peaks and hollows of systolic and diastolic pressures *that is such a pressure as would assure during a certain interval* of time a steady flow of the same amount of blood as passes through a given vessel under the variations of pressure ordinarily found with each heart cycle This mean effective or average dynamic blood pressure gives to be sure a clearer idea than any other reading of the total pressure strain on the cir culation but it has the defects of not taking into account the swing of the pulse pressure which is important and of being difficult to estimate accurately although Vaquez and his associates (1932 and 1933) thought that the maxi mal oscillation of the pulse excursion just above the diastolic level in sphygmo-manometry represents with sufficient accuracy the mean pressure Moreover the mean pressure is usually close to and parallel with the diastolic blood pressure the level of which may be used as an adequate guide along with the pulse pressure Wiggers (1942) called attention again to the mean pres sure but emphasized rather the importance of the pulse pressure

The *pulse pressure* is the difference between the systolic and diastolic pres-sures normally ranging in an adult at rest from 40 mm (for example with systolic pressure of 120 and diastolic of 80) to 70 (for example with systolic pressure of 140 and diastolic of 70)

An abnormal increase of pulse pressure is most commonly due either to an especially high systolic pressure in systemic hypertension (pulse pressure of 120 mm for example with systolic pressure of 220 and diastolic of 100) or to a low diastolic pressure in aortic regurgitation or marked peripheral vasodilatation (pulse pressure of 110 mm for example with systolic pressure of 140 and diastolic of 30) An abnormal decrease of pulse pressure is most commonly found in states of vasomotor shock with or without syncope (15 mm for example with systolic pressure of 65 and diastolic of 50) aortic steno-

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and (*F*) auscultatory gap averaged in a series of 30 cases showing this phenomenon (26 with hyperpiesia 2 with hyperpiesia and aortic stenosis and 2 cases of aortic stenosis without hypertension 205 mm = average systolic pressure 97 mm = average diastolic pressure and * = average auscultatory gap ranging from 177 to 150 mm)

sis (25 mm for example, with systolic pressure of 110 and diastolic of 85) acute or chronic constrictive pericarditis (20 mm for example with systolic pressure of 105 and diastolic of 85) or adrenal insufficiency in Addison's disease (20 mm for example with systolic pressure of 80 and diastolic of 60)

A very abnormal and clinically significant variation of pulse pressure is an alternation found when the heart rhythm is regular or after premature beat (extrasystoles) and due chiefly to a fall in systolic pressure of a few millimeters (2 or 3 to 20) every other beat this is the *pulsus alternans* a sign of serious weakness and probably of alternating strength of contraction of the left ventricle when the pulse is not excessively fast (see Chapters 8 and 30)

The blood pressure in children is less than in adults beginning at about 65 systolic and 40 diastolic in earliest infancy and rising slowly to the adult levels soon after adolescence

Finally it is important to note that the usual blood pressure readings refer to the pressure in the brachial artery on one side It is often wise to measure the blood pressure in both arms (especially if there is suspicion of syphilitic aortitis) and to repeat blood pressure measurements several times at intervals of a few minutes if abnormal readings are found at first The pressure in other arteries of the body varies according to their size position and state of contraction Thus the blood pressure in the aorta is normally greater than that in the brachial artery while that in a digital artery is considerably less. The pressure in the femoral artery is greater than that in the brachial artery for four reasons (1) its larger size (2) the greater bulk of soft tissue mass to be compressed in the leg (3) the lower position of the femoral artery in the body in the upright position hydrostatic pressure thus adding its effect, and (4) a certain amount of compensatory vasoconstriction in the lower part of the body in the erect posture Localized vasoconstriction may occur still further to vary the pressures and sometimes exposure of a part of the body (the arm for example) to cold causes a general vasoconstriction excessive in hypertensive cases and perhaps in potential hypertensive cases (see Chapter 31) Hardness of the arterial wall affects little or not at all the blood pressure readings made by the various indirect methods (Dameshek and Loman 1932 Ayman and Krakower 1933) although loss of elasticity of the walls of the larger arteries favors a larger pulse pressure The act of compression of the arm may itself reflexly affect the first blood pressure levels and not simply from apprehension so that several readings are sometimes necessary I find that it is best for this very reason to inflate the cuff at first only a little above the diastolic pressure and to record that reading during decompression before inflating to a much higher pressure to obtain the systolic reading especially in hypertensive patients

Pulmonary arterial blood pressure During the past few years one of the most desired and needed advances in human physiology has come to pass namely the measuring and recording of the blood pressure in the pulmonary circulation by means of cardiac catheterization and electrical or optical manometer (Dexter et al 1947) (see Figure 18) In fetal life the pulmonary

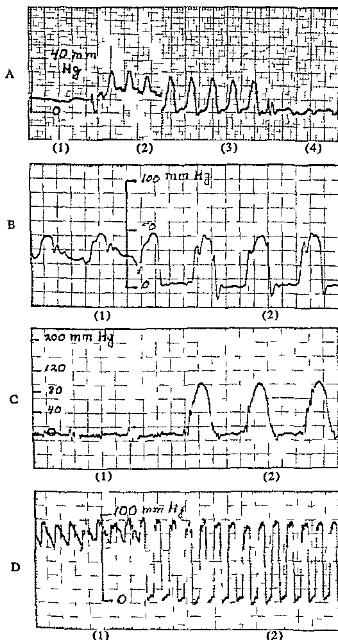


FIG 18 Blood pressure by cardiac catheterization (Kindness of Dr Gordon S Myers Massachusetts General Hospital Boston)

A In a normal 36 year-old man
1 Standardization in millimeters of mercury
2 Pulmonary artery pressure
3 Right ventricular pressure
4 Right atrial pressure

B In a 24 year-old woman with mitral stenosis
1 Pulmonary artery pressure
2 Right ventricular pressure

C In a 19 year-old female with pure pulmonary stenosis of high degree
1 Pulmonary artery pressure—abnormally low with feeble pulsations
2 Right ventricular pressure—very high

D In a 3 year-old girl with tetralogy of Fallot
1 Tip of catheter overriding aorta
2 Pressure in right ventricle

circulation is minimal *but the right ventricle maintains through* the patent ductus arteriosus the major part of the systemic circulation and is larger than the left ventricle Soon after birth when the ductus arteriosus closes the pressures of pulmonary and systemic circuits are undoubtedly very nearly equal, hence at birth it may be said that the pulmonary blood pressure probably measures about 50 to 60 mm of mercury since *that is the systemic* blood pressure at this time Normally the right ventricle fails after birth to maintain the systemic circulation and therefore the pulmonary blood pressure quickly falls below the level of the systemic pressure since the short rapidly dividing pulmonary arterial tree produces relatively little resistance In the human adult the systolic blood pressure in the main pulmonary *artery* measures normally 15 to 35 mm of mercury with average of 25 mm (Figure 18) and the diastolic pressure is about 10 mm of mercury On the other hand when the pulmonary circulatory resistance is much increased as in high grade mitral stenosis left ventricular failure pulmonary endarteritis or severe chronic pulmonary disease the pulmonary arterial pressure rises considerably and may even surpass the systemic arterial pressure as further indicated by the fact that in some cases the right ventricle actually exceeds the left ventricle in size and weight A rough check on the relationship between but not the actual levels of the systemic and pulmonary arterial pressures can be made by comparing the intensities of the aortic and pulmonary second *heart sounds*

Periodic variations of pulmonary blood pressure of considerable extent have been found to occur in experimental animals and also in man with respiration Both systolic and diastolic pressures fall with inspiration and rise with expiration the systolic more than the diastolic Also during cycles of apnea and hyperpnea the pulmonary blood pressure varies *the systolic* pressure falling and the diastolic rising during apnea

Intracardiac blood pressure It has become possible since the publication of the third edition of this book to measure accurately and to record in man the blood pressures in the right heart chambers by intracardiac catheterization *(Cournand et al 1944)* and the use of a manometer *(Hamilton) or* a more recently devised electromanometer (Figure 18) Normally in the human adult the right atrial pressure under as basal conditions as can be attained measures from +2 or +3 to −2 or −3 mm of mercury averaging 0 mm and the right ventricular pressure ranges from +15 to +35 systolic and from 0 *to +2 mm diastolic The pressure in the left heart chambers is* as yet not determinable normally but the left atrial pressure has been measured directly in the case of a congenital atrial septal defect being about +5 to +10 mm of mercury therewith and at operation in mitral stenosis being found to measure about +30 mm varying with the degree of valvular obstruction

Venous blood pressure The venous blood pressure was measured two hundred years ago by Hales who inserted a manometer directly into the jugular vein of a mare (Hales 1733)—see quotation at the beginning of this chapter The venous blood pressure may be measured with a fair degree of accuracy as has been shown by ascertaining the actual pressure level vertically above

the level of the junction of the superior vena cava and the right atrium (approximately one third the distance through the chest from front to back at the lower border of the third right sternocostochondral junction) to which blood will rise or displace normal salt solution in a tube connected by trocar or needle with an arm vein (Moritz and von Tabora 1910 Holt 1940) or more conveniently by a spring phlebomanometer connected with the vein (Burch and Winsor 1943) In logical evolution from these cruder technics the newest and most accurate though not exactly routine method of venous blood pressure measurement is by intravenous catheter and special electromanometer

A simple but generally adequate clinical method of determining the

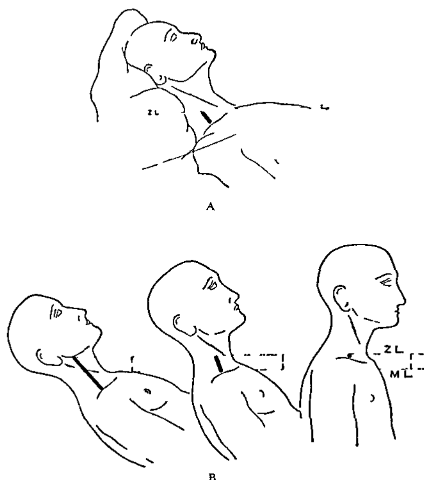


FIG 19 The level of the height of the blood column in the jugular vein (*A*) In a normal person recumbent (*B*) In a person with increased systemic venous pressure in different inclinations of the body Z.L = zero level M L = manubrial line (Lewis, T *Diseases of the Hea t* 4th ed The Macmillan Company New York 1946)

venous pressure requiring no apparatus except a centimeter scale is t measure the height above the lower border of the third costal cartilage at th right border of the sternum (level of mouth of the superior vena cava) which the blood rises in the jugular vein with the subject sitting upright the pressure is within the normal range that is below 10 cm the vein wi not be evident and if it is very high that is above 25 cm the blood colum will rise out of sight under the ear slight to moderate elevations can readily measured (Figure 19) A third but now outmoded method is determining the amount of air pressure (best measured in centimeters water) necessary to collapse a superficial vein of moderate size in forearm hand An apparatus for making such a measurement has already been men tioned (page 110) Obesity thick skin or sclerosis of the veins may mal such determination difficult

The normal venous pressure varies widely from 4 to 10 cm of water (about 1½ to 6 mm of mercury) Usually it amounts to about 6 to 7 cm of water being about one half in millimeters of water of the normal arterial pressure in millimeters of mercury and therefore about 1/20 of the arterial pressure The systemic blood pressure thus drops from say 130 to 5 mm of mercury as it progresses from brachial artery through its branches and through ar terioles capillaries and venules to a superficial vein of moderate size on the back of the hand or on the forearm If the venous pressure by the usual method measures 10 cm or more of water it is abnormally high Exercise may tem porarily raise the pressure considerably even as high as 20 cm of water but the three conditions which are associated with abnormally high venous pressure at rest, even to 30 cm of water or more are congestive heart failure of considerable or moderate degree acute or chronic constrictive pericarditis and venous obstruction due to thrombosis or compression If the right ventricle remains competent while the left ventricle has failed there is pulmonary con gestion and increased pulmonary venous pressure due to left ventricular weak ness even though the systemic venous pressure remains normal

A very interesting phenomenon is encountered in some cases with well marked tricuspid regurgitation without much constant distention of the sys temic veins, consisting of a considerable *systolic jugular pulse* most pro nounced in the deep veins in the neck In such cases the venous pulse pressure which is usually very small or nonexistent may be marked up to 50 or 60 mm and so striking that the jugular pulse may be wrongly interpreted as the carotid pulse (White and Cooke 1939)

Another interesting phenomenon consists of the *paradoxical inspiratory filling of the jugular veins* due to the inability of the right heart chambers either because of constrictive pericarditis or severe right heart failure or of an obstructed superior vena cava to pass on the extra blood they receive from the systemic veins as the result of the increased negative intrathoracic pres sure during inspiration (Hitzig 1942)

In general the venous pressure determination is not of great clinical value inspection of the veins to determine their degree of engorgement usually sufficing without exact measurements It has been suggested however that a

figure of 20 cm of water of venous pressure in heart failure is a useful indication of the therapeutic need and value of venesection

We can now measure the blood pressure in the great veins in man by catheter and special manometer It varies normally in the human adult from +3 to +5 mm of mercury with great increase when the heart fails or in chronic constrictive pericarditis In the experimental animal the blood pressure in the great veins has been found to be much lower than that of the smaller veins dropping almost to zero in the venae cavae This is to be expected with the slowing of the blood stream resulting from the merging of many venous channels into the narrow limits of a few for even though these few are of large caliber their total capacity is far less than that of the peripheral veins Fortunately to aid in the return of blood to the heart there are four factors the most important of which is the intrathoracic negative pressure The effect of intrathoracic suction during inspiration is marked and in the experimental animal may more than quadruple the actual venous pressure in the great veins to establish the effective venous pressure For example in the dog a venous pressure of 10 mm (1 cm) of water may be increased through the action of this negative intrathoracic pressure to an effective pressure of 50 mm of water in the right atrium Poor action of the diaphragm and disturbances of respiration limiting the negative intrathoracic pressure and especially obstruction to the venous return flow to the heart through congestive heart failure chronic constrictive pericarditis pericardial effusions or mediastinal tumors or adhesions affect very easily and obviously the venous blood return to the heart on account of the low pressure that is usual in the great veins This is particularly true of the portal system where the blood has to flow through two sets of capillaries and enter the inferior vena cava by way of the hepatic veins which empty at a considerable angle into the vena cava

The three other factors aiding the return of venous blood to the heart are the tonus and movement of muscles which compress the veins the valves in the veins which help to keep the blood going in the right direction and on occasion as needed arteriolar and capillary dilatation to allow a speeding up of the blood flow into the veins and thence to the heart

For a discussion of capillary blood pressure see Chapter 8 under Capillary Circulation

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CHAPTER 7

CARDIOVASCULAR ROENTGENOLOGY

In the present edition this chapter has been profitably shortened several helpful new illustrations have been added and a number of pertinent references to the literature published since 1943 have been appended to the Bibliography

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During the past two or three months I have been much interested in studying the X rays and with the assistance of Mr C L Norton and Mr R R Lawrence of the Massachusetts Institute of Technonogy who have been investigating the X ray problem in the Rogers Laboratory of Physics have tested the application of X rays to medicine in various ways Their application to surgery was soon evident

But I wish especially to direct your attention to some of the medical rather than the surgical uses of these magical rays and especially to their use with the fluoroscope in the fluoroscope with a screen of tungstate of calcium the parts of the body which are most easily passed by the X rays appear lightest on the screen those which are densest being darker The lungs are easily penetrated

The pulsations of the heart may be followed with the fluoroscope not only the ventricular but also the auricular contractions and dilatations

In the following cases the usual physical examination and that made with the fluoroscope corresponded very well

Case I —The first medical case I examined was that of a man with an enlarged heart (seven inches in transverse diameter) I found that the outline of the heart as seen from the front of the body through the fluoroscope corresponded in a general way to the outline drawn on the skin with percussion as a guide It was interesting to note that the heart could be made out through the man s waistcoat and two shirts

INTRODUCTION

Cardiovascular roentgenology (*Rontgen* 1895 and λογος knowledge) or radiology (*radius* ray and λογο knowledge) has become firmly entrenched as an important part of routine study of the heart and blood vessels it ranks

fourth in value as a method of examination after history taking physical examination and electrocardiography Although in cardiovascular diagnosis the roentgen ray usually supplies but confirmatory evidence sometimes surprising and frequently useful and interesting information results from such routine study Only by this method may the size and shape of the heart be determined with certainty during life the size and shape of the left atrium aorta and lung hiluses be ascertained at all and calcification in pericardium heart muscle valves or deep blood vessels be actually visualized On the other hand

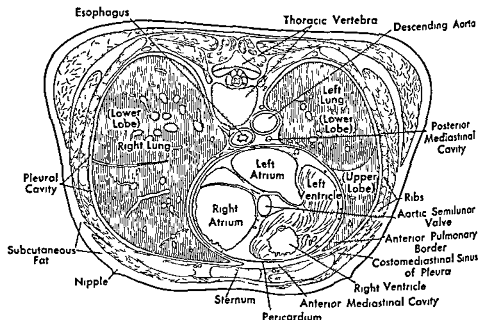


FIG 20 Anatomic drawing showing cross (horizontal) section of thorax and heart at level of the eighth thoracic vertebra (Sobotta and McMurrich *Atlas and Textbook of Human Anatomy* 1906 Kindness of W B Saunders Company Philadelphia)

it must be admitted that serious heart disease may be present as discovered in other ways when no clue is given to its presence by roentgenology Also early and slight cardiovascular lesions usually escape notice in the roentgen ray film because the heart and vessels may show no definite abnormalities of size shape, or action For the most part therefore roentgenology merely reveals evidence of well established or advanced disease which is difficult or impossible to eradicate Yet it does help the practitioner of medicine appreciably in the establishment of exact diagnosis which are so essential to accuracy of prognosis and to the handling of patients with chronic heart disease

The chief difficulty in the routine application of roentgenology to the circulation lies not in the technic which can be mastered without great difficulty but in the interpretation of the normal limits of heart size shape and action and therefore in the diagnosis of slight abnormalities There are so many factors for example age size build respiration and nervousness resulting in in

dividual variations within the normal (see Figures 2 3 and 6 in Chapter 2) that it is at present impossible to recognize them all or at least to take them all into consideration in the establishment of any satisfactory tables of measurement of size or rules about shape or action Not only are the normal limits difficult or impossible to define accurately but in a given individual important changes may occur in heart size or shape insufficient to produce definite roentgenologic abnormalities at the time of examination which would be noted if comparative studies had been previously made For example a heart showing in an anteroposterior teleroentgenogram a *shadow area of 80 sq cm* at the lower limit of the normal figures may increase in area 38 per cent before it equals even the average normal measurement (110 sq cm) and as much as 75 per cent before it equals the upper normal limit of 140 sq cm in the case of a person with a body surface area of 1 8 sq meters (Smith and Bloedorn 1922) Successive records of heart size and shape in the same individual carefully made under varying conditions of health should be more useful than a single comparison of this individual case with a table of normal averages or a set of rules it is however often impossible to possess information about the roentgen ray findings prior to the onset of trouble in a given case In spite of these difficulties some rules are necessary and normal standards for measurements of size are useful if we realize their inaccuracy in application to individual patients and do not lull ourselves into a false sense of security which tends to develop from the use of figures and formulas

METHODS OF CARDIOVASCULAR ROENTGENOLOGY

Roentgenology of the heart includes seven procedures the first three of which are commonly used and the last four in special cases or for some particular study They are as follows (1) fluoroscopic examination (2) orthodiagraphy (3) teleroentgenography (teleradiography) (4) (roentgen) kymography (5) (roentgen) tomography (planigraphy) (6) visualization of heart chambers and greater and lesser arteries and veins by the injection of radio-opaque media (e g Diodrast) into the blood stream and (7) roentgencinematography At the present time the first method is used universally by the most careful workers everywhere but the other methods are rarely used together There is a division into two schools that employing orthodiagraphy and that using teleroentgenography Each of these methods has certain advantages which will be presented below but in each case fluoroscopy should be and ordinarily is employed along with either orthodiagraphy or teleroentgenography The seven procedures mentioned above will be briefly summarized herewith

1 **Fluoroscopy** (φλύειν to flow out ῥοή current and σκοπεῖν to examine) Fluoroscopic examination consists in the study on the fluorescent screen of the projection of the heart shadow in its various parts and in toto and with the thorax of the subject in various positions in contact with the screen If possible the subject should in harmony with several other methods of ex

amination—inspection percussion and auscultation—be examined chiefly in the upright position Although the tube may be placed at a distance (2 meters or more) from the thorax for the purpose of seeing the heart and great vessels relatively undistorted by divergence of rays (telefluoroscopy), as in the case of teleroentgenography this is not essential inasmuch as accurate measurements can be obtained by orthodiagraphy nor is it practicable since so much extra energy is required (about 16 times as much as is needed with the tube at 50 cm) In fact the very magnification of the details and activity of the heart shadow by the divergent rays is helpful and one quickly becomes accustomed to the degree of distortion Also the illumination is better with the tube nearer than at a distance especially in the oblique or lateral views

The first position studied is most conveniently the *anteroposterior*[1] with the patient erect facing the observer squarely and leaning his anterior chest wall against the screen with the tube behind him After all parts of the heart and great vessel shadows have been carefully examined in this position the contour and action of the whole heart observed the action of the diaphragm noted along with the effect of deep inspiration and expiration and the lung shadows and especially the hiluses studied the patient should then be rotated slightly to the left so that the right anterior side of the chest wall touches the screen This is called the *right anterior* or *first oblique position* To improve the view in this position the right hand should be held behind the head and the left hand on the left hip with the elbow forward Still further rotation in the same direction to the *right lateral* and *right posterior oblique positions* may then be carried out if desired but this is usually not necessary study in the right anterior oblique position sufficing In a similar way the patient is rotated to the right from the anteroposterior position until the left anterior part of the chest wall touches the screen This is called the *left anterior* or *second oblique position* The left hand should be held behind the head and the right hand on the right hip Again further rotation in the same direction may be carried out if desired to the *left lateral* and *left posterior oblique positions* And finally the patient may be examined with his back squarely against the fluoroscopic screen in the *posteroanterior position* to emphazie abnormalities of the descending thoracic aorta but this position is rarely of any value For routine fluoroscopic examination the three positions anteroposterior right anterior oblique and left anterior oblique ordinarily suffice An important part of the whole examination includes careful observation of heart and vessel shadows during the process of rotation from one position to another this may explain certain abnormalities the cause of which is not obvious in the positions themselves Fluoroscopic tracings not orthodiagraphic are sometimes

[1] Throughout the book the position of the subject in roentgenologic examination is designated according to the axis termination at the screen or film as has been customary and not at the tube thus anteroposterior signifies that the front of the chest rests against the screen "right anterior oblique means that the right anterior chest wall is against the screen and so on If the designation "posteroanterior is employed in the place of the customary "anteroposterior" "left posterior oblique must be similarly employed instead of right anterior oblique to be consistent but this change is neither necessary nor convenient

made in one or more positions to study outline shapes but these are of limited value

2 Orthodiagraphy (ορθως straight δια through and γραφειν to write) (Moritz 1902) An orthodiagram is a tracing made by the observer of the shadow of the heart and great vessels outlined against the fluoroscopic screen by the *central rays* from the roentgen tube Its advantages are that it is very accurate if well done because the rays used are exactly parallel that observation of the heart in action allows accurate determination of the position of the apex and of junctions of atria and ventricles or of great vessels and heart which may not be possible in any other way that it requires fluoroscopic observation not always carried out with teleroentgenography and finally that it is an inexpensive method of obtaining permanent records of the shadow of the heart and great vessels It has the disadvantages of incompleteness of total detailed picture of heart and thorax and of easy possibility of subjective errors in untrained or careless hands

3 Teleroentgenography (τηλε far away *Rontgen* the discoverer and γραφειν to write) or teleradiography (Kohler 1905) The other method in routine use for obtaining a graphic record of the heart shadow by roentgen ray from which a fairly accurate idea of heart size and shape can be obtained is teleroentgenography (teleradiography) A teleroentgenogram is a record on film or plate of the shadow in whole or in part of the heart and great vessels cast by the roentgen rays with the tube far enough away (2 meters or 6 to 7 ft) from the chest and plate for reasonable accuracy At 6 to 7 ft the error of heart size measurement is however still appreciable the excess in transverse cardiac diameter in the normal adult being from 1 0 to 1 5 cm (8 to 12 per cent) and as great sometimes in pathologic cases as 2 5 cm the excess is still more evident in the measurement of surface area Certain factors enter in as variables to increase or to decrease this error They are chiefly heart size and thickness of the anterior chest wall The larger the heart the greater is the error because the rays outlining its shadow are more divergent than are those outlining the shadow of a small heart Even the ratio of heart size to thorax size (the cardiothoracic ratio) differs in the two technics being slightly less in teleroentgenography than in orthodiagraphy because the maximal frontal plane of the heart lies anteriorly to that of the thorax (see Figure 20 page 126) The advantages of the teleroentgenogram are as follows (1) it is a more objective record than an orthodiagram and so less liable to subjective sources of error provided the technic be accurate (2) it is a more complete record than the orthodiagram giving greater detail and demonstrating clearly differences in position of the thorax which differences may render inaccurate comparative measurements of heart size at different times (3) it outlines more clearly hazy or otherwise indefinite borders (4) it can be satisfactorily carried out by a well trained and careful technician the actual measurements and interpretation being made from the finished film by the physician

4 Kymography (κυμα wave and γραφειν to write) About twenty years ago there was introduced (Stumpff 1931) an ingenious application of roent

genography to the study of the degree and direction of pulsation of the heart and great vessels first suggested by Sabat (1913) By the use of a grid of lead strips with narrow slits between them it is possible to record the systolic and diastolic heart and vessel borders of limited alternating sections of the heart shadow when the film moves at a uniform rate across the slits at a speed which allows several pulsations to be recorded for each of the shadow sections The grid may be placed vertically, diagonally or radially and the screen or the grid may move in any direction but the usual and most practicable and instructive arrangement is for the grid to be fixed in place with the slits horizontal and for the film to descend vertically In the resulting kymogram (see Figure 21) the innermost limits (valleys) of the excursions normally represent systole in the case of the heart shadow and diastole in that of the shadows of the great vessels while the outermost limits (peaks) normally represent diastole in the case of the heart shadow and systole in that of the shadows of the great vessels In certain disease conditions there are distortions of these pulsations an increase, for example in cases of aortic regurgitation so far as left ventricle and aorta are concerned, or of the whole heart and both aorta and pulmonary artery in thyrotoxicosis a decrease in cases of great myocardial weakness myxedema or constricting pericardium or an absence or even a reversal of the pulsation (called paradoxical) of a limited portion of the left heart shadow border at or more often just above the apex in the case of a moderately large cardiac aneurysm or myocardial infarct There is not a great deal of clinical value in roentgenkymography except in occasional confirmation or discovery of a myocardial infarct from coronary occlusion the differentiation at times of aortic aneurysms from other types of mediastinal tumors the separation of the shadows of atria and ventricles and in the course of complete study of rare or puzzling cases

An interesting new method of recording the action of the heart fluoroscopically has been introduced through Chamberlain by Henny and Boone (1945) by the use of the photoelectric cell placed over any desired portion of the heart border and connected with galvanometer Simultaneous tracings can be made of the electrocardiogram or of carotid pulse or heartbeat itself also recorded electrically Figure 22 shows examples of normal and abnormal curves which have been variously called *electrokymograms* or *electrofluorograms* Not only may records be made of the pulsation of atrial and ventricular borders and of that of the great vessels superior vena cava aorta pulmonary artery and its branches in the lung hiluses but so-called *densograms* can also be made over the main heart shadow itself and over the lungs presenting curves of the variations in the thickness of the underlying mass These electrokymograms present a clearer and simpler record of the cardiovascular motions than the films that have been customarily taken in the past (Figure 21) and will probably supersede them They have the same function however in revealing or confirming such diagnoses as myocardial infarction of significant extent and of certain aneurysmal dilatations of the great vessels Also they have been used in an effort to measure the stroke volume of the heart

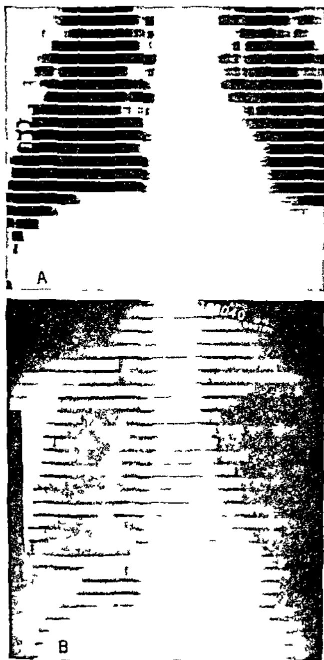


FIG 71 Kymograms (roentgenograms) of thoraces of (*A*) normal individual (kindness of Dr Richard Schatzki Mt Auburn Hospital Cambridge Mass) (*B*) case with myocardial infarct (kindness of Dr George Levene Massachusetts Memorial Hospital Boston)

5 **Roentgentomography** (*Roentgen* τομος a cut or section and γραφειν to write) or laminagraphy (Latin *lamina* layer and γραφειν), or planigraphy (Latin *planus* a level and γραφειν) There has also been introduced in recent years a method of x ray study of the thorax that is helpful particularly in locating in three dimensions the exact position of lesions in the lungs It is of much less importance so far as the heart is concerned but the method has not in that direction been wholly explored as yet Tomography consists in the

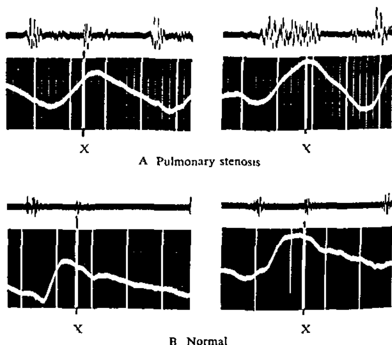


FIG 22 Electrokymograms and simultaneous phonocardiograms taken at the pulmonary valve area of (A) two patients with pulmonary stenosis and (B) two normal individuals Note the slow upstroke in the electrokymogram of the two patients with pulmonary stenosis Time = 0 04 and 0 20 second X = time of second heart sound (Kindness of Mr M A Rappaport Sanborn Company Cambridge)

recording of body shadows at varying depths by exact focusing of the x rays —thus the anterior and posterior regions of the thorax may be blurred while a sharp outline is obtained of a vertical frontal plane in midthorax It is possible by this means to obtain clearer pictures of the atria and pulmonary vessels or of the aortic arch or descending aorta

6 **Radio opaque visualization** In obscure or special cases the injection of a radio-opaque medium most commonly Diodrast into veins or arteries of arms or legs and very recently even directly into the ventricles themselves (Ponsdomenech and Nuñez 1951) has proved helpful in establishing a detailed diagnosis of abnormalities of blood vessels or heart chambers that might be impossible in any other way (*Figures 23 24 and 148 page 779*) Considerable experience in both injection and roentgenographic technic is neces



FIG 73 Roentgen films of chest of male age 40 with shadow in region of aortic arch (*A*) Anteroposterior view (*B*) Left anterior oblique view immediately after Diodrast injection showing filling of right ventricle and pulmonary arterial tree (*C*) Film a few seconds later showing filling of the left ventricle and aorta This method of technic of Diodrast injection establishes at once the diagnosis of mediastinal tumor versus aortic aneurysm (Kindness of Dr B J Walsh Washington D C)




A




B

FIG 24 (*A*) Diodrast x ray pictures showing the filled right ventricle and pulmonary artery in the anteroposterior and left anterior oblique views in the case of a normal heart (*B*) Diodrast x ray pictures showing the filled left ventricle in the case of a normal heart with diseased right lung (Kindness of Dr E R Ponsdomenech and Dr V B Nunez Havana Cuba)

sary to obtain the best results but the method should be made available in every teaching hospital and is helpful in differential diagnosis especially in congenital heart disease

7 Roentgencinematography Finally a seventh method of roentgen ray study of the heart of interest from the standpoint of special investigation or teaching is that of cinematography The most practicable way which has recently been developed consists of cinematography of the shadow as it is seen on the fluoroscopic screen (Reynolds R J 1934 Janker R, 1936 Rushmer 1949)

THE SHAPE SIZE AND ACTIVITY OF NORMAL HEART AND GREAT VESSELS STUDIED BY ROENTGEN RAY

The shape of the normal roentgen ray heart shadow is quite variable being dependent on a number of factors The heart shadow should be outlined during quiet respiration and preferably in the sitting position for forced respiration causes abnormalities of shape and size and the standing and recumbent positions may appreciably affect the heart Marked changes have been experimentally produced by certain respiratory efforts the heart shadow increasing considerably in size with the Muller experiment (an attempt to inspire forcefully with the glottis closed) and decreasing considerably in size sometimes to appear like the cor pendulosum (pendulum heart) with the Valsalva experiment (an attempt to expire forcefully with the glottis closed) a fact of considerable interest (Crowden and Harris 1929) such experiments produce however very artificial conditions not comparable to clinical findings The decrease in heart size during the Valsalva experiment is due to the prevention of entrance of blood into the heart by the increased intrathoracic pressure while the increase in heart size during the Muller experiment is due to the increased flow of blood into the heart resulting from the markedly negative intrathoracic pressure So far as position of the subject is concerned the heart size and therefore its shadow may be considerably decreased in the standing position (due to much decrease in the return of blood to the heart in that posture) while there may be a considerably increased return of blood to the heart and increased content of blood in the lung vessels in the recumbent position resulting in a physiologic dilatation (Zdansky 1936) In reporting or recording roentgen views of the heart a statement should always be made as to the position of the patient and also the phase or state of respiration To study the heart (in contrast to the lungs) it is best to make the examination and the films during very quiet respiration which is essentially midway between full inspiration and full expiration There can be great distortion of the heart shadow with marked decrease in size if the films are taken while the breath is held in full inspiration a common practice in study of the lungs (Figure 3C page 32) For further observations concerning the range of the normal heart the reader is referred to Chapter 2

Anteroposterior view In the anteroposterior view the shadow of heart and

great vessels is roughly egg shaped with apex diagonally down and to the subject s left and with the great vessels attached as a pedicle at the left side of the base (Figure 25) If the diaphragm is high the heart lies more horizontally and to the left and there is a more acute angle between it and the great vessels (Figure 3 page 32), if the diaphragm is low the heart lies more vertically and centrally in the body seems narrower (because of this change of position and of the resultant rotation to the left) and hangs down from the great vessels with much flattened angle (Figure 3)

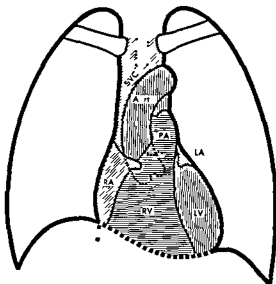


FIG 25 Drawing of normal x ray heart shadow with the various chambers and great vessels indicated (Kindness of Sir John Parkinson and the *Lancet* London)

SVC superior vena cava
PA pulmonary artery
RA right atrium
RV right ventricle
LA left atrium
LV left ventricle

The borders of the anteroposterior shadow of the heart and great vessels are three in number because of the roughly triangular shape they are right left and inferior Unless concealed by abnormal shadows in lungs pleurae pericardium or mediastinum the right and left borders are easily seen The inferior border is seen with difficulty or not at all concealed as it is by intra abdominal shadows unless there is sufficient air in stomach or intestines to make its outline visible Its whole extent is seen in only two conditions (1) pneumoperitoneum and (2) interpolation of colon between heart and liver The upper border of the heart at the junction of the great vessels is not seen except at its outer ends

1 *The right border* (that to the right of the sternum of the subject not on the observer s right) is composed of three parts The uppermost is a rather faint straight vertical edge extending slightly outward and to the right from below up and not always clear It is produced by the shadow of the

right border of the superior vena cava and innominate vein at the upper part overlying the innominate artery the artery itself if dilated or prominent may form the shadow edge The second part (next in order below) is the straight edge of the superior vena cava or more commonly the slightly convex shadow of the right edge of the ascending aorta superimposed on the superior vena cava shadow and making up a second quarter or more of the whole right border the inwardly directed curve of this aortic shadow to the left can often be made out overlying the fainter shadow of the vena cava The third part of the right border of the heart shadow is the moderately convex shadow of the right edge of the right atrium from a point just below the mouth of the superior vena cava down to the inferior vena cava which can in rare instances be barely seen as a very short straight line quickly disappearing into the shadow of the diaphragm this right atrial shadow makes up the lower third to half of the right border of the shadow of the heart and great vessels

2 *The left border* of the shadow of the heart and great vessels is considerably longer than the right (about 50 per cent longer) and is made up normally of four parts The uppermost part is a short convex curve close to the apex of the whole shadow and is directed up toward the left shoulder of the subject it is variable in prominence and is due to the shadow of the upper and left edges of the aortic arch and beginning of the descending aorta The second part is a slightly convex curve just below usually slightly longer than the first but making a considerable angle with it directed downward from the subject s right to his left and often almost continuous in direction with the left border of the main shadow of the heart itself which lies below the trunk of the pulmonary artery and its left main branch cause this convexity Third and next below for a very short distance and forming a straight or slightly convex line lies the left border of the left atrial appendage often not distinguishable from the edge below it unless its presystolic pulsation happens to be seen or there is marked left atrial bulging And fourth the major part, two thirds to three fifths of the left heart and great vessel shadow border is caused normally by the left ventricular shadow forming a slightly or moderately convex line sloping to the subject s left from above downward and becoming more definitely curved downward as the apex is approached

3 When *the lower border* of the heart shadow is visible it is made up of the apex and lower border of the left ventricle on the extreme left then for one half to three quarters of the distance to the subject s right heart border it is caused by the right ventricular shadow and for the rest of the distance to the right of the midsternum by the right atrium However varying positions of the heart alter these relations for example in the case of the drop or vertical heart little or none of the right atrium forms the lower border of the heart shadow When this lower border is visible it is slightly convex near the apex but fairly straight from there on

The peak of the heart and great vessel shadow is blunt and obscure except where the aortic arch is visible on the subject s left, but in some cases the aorta crossing above the pulmonary artery to form the arch can be seen This

peak of the great vessel shadow is more cylindric than cone shaped being an elongated pedicle

Right anterior oblique view In the right anterior or first oblique view (Figure 26) the shadow of the heart and great vessels shows in front from below upward the convex curve of the right ventricle if the subject is sufficiently turned if the rotation is slight the left ventricle may be seen At the upper third of this anterior edge the pulmonary artery and aortic shadow appear and the latter sweeping over in a long curve loses itself in the shadow

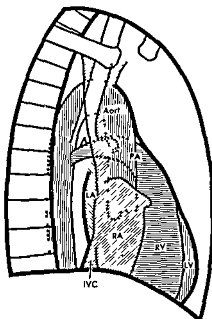


FIG 26 Drawing of shadows of normal heart and great vessels in right anterior oblique position with various chambers and great vessels indicated (Kindness of Sir John Parkinson and the *Lancet* London)

IVC inferior vena cava
PA pulmonary artery
LA left atrium
RA right atrium
RV right ventricle
LV left ventricle

of the spine posteriorly Under this aortic shadow and at the upper part of the posterior border of the heart shadow lie the bifurcations of the trachea and of the pulmonary artery Below this are the straight or slightly convex borders of the two atria the left above the right and the latter extending down to the diaphragmatic shadow where the inferior vena cava may be just visible The anterior and posterior mediastinal spaces should be clear and the trachea and bronchi are usually to be seen The left ventricle is concealed at the back of the heart shadow in this position (note Figure 20)

Left anterior oblique view In the left anterior oblique view (Figure 27) the heart is seen as it were almost in sagittal section both ventricles and both atria being evident the two former making up the lower two thirds of the

heart shadow the right in front and the left in back and the two latter making up the upper third of the shadow, the right in front and the left behind The aorta arches over the top its whole extent may be seen better in this view than in any other if it is sclerotic but normally the outline of the lower border of the aortic arch is made out with great difficulty if at all Below the aorta at the upper limit of the heart shadow posteriorly is the pulmonary artery Between the aortic arch and the pulmonary arch is a clear space called the aortic window

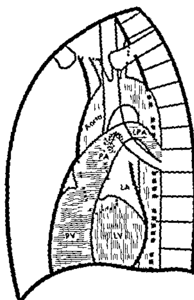


FIG 27 Drawing of shadows of normal heart and great vessels in left anterior oblique position with various chambers and great vessels indicated (Kindness of Sir John Parkinson and the *Lancet* London)

PA pulmonary artery
LPA left pulmonary artery
LA Left atrium
RV right ventricle
LV left ventricle

Note aortic window (open space) separating aortic arch from pulmonary arteries

The chief advantage of the oblique views lies in the study of aorta and left atrium this is especially true of the left anterior oblique view which has been regarded by some workers as the most valuable of all views in establishing the comparative size of the various parts of the heart

Lateral view The lateral view is of value in measuring the depth that is the anteroposterior diameter of the heart for its own value or for use in a formula to estimate the heart volume (see page 146) This diameter is taken at right angles to the long axis of the heart

Normal size of heart and great vessels Certain measurements of heart size made on the orthodiagram or teleroentgenogram are in routine use and are of some value in spite of the wide normal variations and of the difficulty or

impossibility of judging accurately either the presence or degree of slight cardiac enlargement by such measurements It is obvious for example that increase in heart volume is represented by a far smaller increase in measurements of diameters or of area an increase of 100 cc of volume would add only about 15 sq cm to the area in the anteroposterior view

The following are the more useful teleroentgenographic measurements all but two obtained in the anteroposterior view to make correction for orthodiagraphic records subtract 10 per cent Other measurements of all sorts have been suggested but only the more important or interesting will be mentioned here

The *transverse diameter* of the heart (T or H—Horizontal—of Bordet) is made up of the sum of the maximal distance of the right border from the midsternum (MR) and of the maximal distance of the left border from the midsternum (ML) Normally this diameter measures in the adult from 10 to 15 cm depending on the size of the person and from 6 to 10 cm in the child

The *long diameter* of the heart (L) is the distance from the junction of right atrial and great vessel shadows on the right border to the point of the cardiac apex Normally this diameter measures in the adult 1 0 to 1 5 cm more than the transverse diameter on the average therefore from 11 to 16 cm and in the child 0 5 to 1 0 cm more than the transverse diameter that is from 7 to 11 cm

The *broad diameter* of the heart (B) is made up of the addition of the lengths of two perpendiculars dropped from the line of the long diameter to the junction of right atrial shadow and diaphragm on the right (BR) and to the junction of left atrial (or left ventricular) and pulmonary artery (or right ventricular) shadows on the left (BL) Normally this diameter measures in the adult 8 to 11 cm and in the child 5 to 8 cm

The *left ventricular chord* (LV or VG—*ventricule gauche*—of Bordet) subtends the arc of the left ventricle from its upper extremity on the left to the apex Normally this chord measures in the adult from 5 to 9 cm and in the child from 3 to 5 cm

Width of the great vessels (GV) A measurement of some interest but not of much value is that of the width of the shadow made by the great vessels at the widest part of the pedicle of the heart shadow usually at the level of the second intercostal space horizontally measured This measurement varies not only with dilatation of the aorta and superior vena cava but also with kinking of the aorta when it is very tortuous from arteriosclerosis or pushed upward by an enlarged or horizontally placed heart resting on a high diaphragm Normally the width of the great vessels measures 5 to 7 cm in the adult and 3 to 4 cm in the child of ten years of age

The *diameter of the aortic arch* (Ao) taken in the anteroposterior position is a measure of the length of the horizontal line drawn from the outermost bulge of the aortic shadow at the left of the midsternum to the shadow of the barium filled esophagus which passing under the aortic arch outlines

he right border of the descending portion of the arch a subtraction of 2 mm s necessary to take into account the thickness of the wall of the esophagus If this line is not horizontal the measurement is inaccurate because of abnormal relative positions of aorta and esophagus The normal upper limit of this aortic arch measurement in the adult should not be over 3 cm The diameter of the aorta at the beginning of the arch (Ao or Asc A) is found in the right anterior oblique position by measurement of the horizontal line joining the two sides the anterior edge outlined by the anterior mediastinum and the posterior edge by the trachea Two millimeters comprising the thickness of the tracheal wall should be subtracted from this measurement to obtain the true aortic diameter which should normally range from 2 5 to 3 5 cm at this point An unsatisfactory measurement of the diameter of the aortic arch is that obtained in the left anterior oblique position namely the vertical distance from top to bottom of the aortic arch shadow at the top of its curve This in the normal adult averages 3 0 to 3 5 cm It is unsatisfactory because often the lower border of the aortic arch is seen only with great difficulty if at all unless a contrast medium has been injected

The *depth of the heart* (or anteroposterior diameter) is measured at right angles to the long axis of the heart in the lateral view at the point of greatest thickness Normally this measures two thirds to three quarters of the transverse diameter of the heart in the anteroposterior view (Roesler 1934) or in the adult 6 5 to 10 5 cm and in the child 4 to 7 cm Its chief value is in checking the significance of the measurement of the diameters of the anteroposterior view and in forming a part of a formula for estimating the volume of the heart

A standard but often unsatisfactory measurement of chest size for comparison with heart size is the *internal diameter of the thorax* (Th) at its widest point just above the diaphragmatic attachment

The *area* of the heart shadow (A) which does not include the great vessels is measured after arbitrarily joining by slightly convex lines the outer and visible ends of the upper and lower borders The area can be easily determined by the use of a planimeter less easily by superimposition of cardiac outline on paper specially ruled with centimeter squares or by weight of paper cut out exactly to fit heart shadow compared to weight of 100 sq cm of the same paper (Mazer 1942) but most easily by nomogram based on the broad and long diameters of the heart (Ungerleider and Gubner 1942) The area of the normal heart shadow in the anteroposterior teleroentgenogram measures in the adult from 65 to 145 sq cm averaging 112 for males and 100 for females and in the newborn from 17 to 20 sq cm

Finally attempts have been made to obtain a measurement of *heart volume* by the use of various formulas Such measurement theoretically ideal has not as yet proved practical it will be discussed below The range of the normal heart volume in the adult male is from 400 to 900 cc and in the adult female from 300 to 550 cc (Comeau and White 1939)

When the heart lies horizontally the transverse and long diameters become more nearly the same A correction of the normal transverse measurement for

position has been suggested based on the angle between the lines of these two diameters and utilizing the surface area of the body for standard comparison. The smaller the angle and also of course the larger the surface area of the body the longer should be the transverse diameter Figure 28A shows the average normal measurements of the transverse diameter with these two variables charted and Figure 28B shows the surface area of the subject in square meters calculated according to height and weight This latter figure may also be used in calculating the normal vital capacity (see Chapter 10)

The relationship of depth or thickness of the heart to the size of the area and diameters on the frontal plane silhouette is of much interest and of fundamental importance The flatter the chest the less is the depth of the heart and the greater are the various frontal plane measurements the deeper the chest the smaller should be the frontal plane measurements of the heart (Roesler 1934)

Calculation of normal heart measurements The simplest most practical, and most reliable heart measurements are those of the *diameters* transverse long broad and anteroposterior (or depth) They are measured directly and usually with ease The transverse diameter is the most useful of the diameters, the anteroposterior the least used Tables slide rules and nomograms (Hodges and Eyster 1926 Ungerleider and Gubner 1942 Kurtz 1943) have been constructed for the calculation of the normal average transverse diameter according to height and weight for comparison with the actual finding in any given case (Figure 29) The range of normal varies from 10 per cent above to 10 per cent below this figure a fact that materially diminishes the value of this as well as all other roentgen measurements as utilized at present (see Chapter 2)

A roentgen measurement of heart size very popular in the past but generally unreliable and unsatisfactory because of the extremely wide range of the normal (from 33 to 57 per cent) is the so-called *cardiothoracic ratio* or *heart lung quotient* using a fraction in which the numerator is the transverse diameter of the heart and the denominator the internal diameter of the thorax the normal range is from 0 33 to 0 55 Not only is the range of normal too wide because of the poor correlative standard of thoracic width (height and weight are preferable although also open to objection) but the cardiothoracic ratio has in addition the defect inherent in the transverse diameter which does not take into consideration the broad diameter of the heart which may be considerably increased in mitral stenosis for example without increase in the transverse diameter There are however rare persons of unusual build short and light with wide chests in whom the cardiothoracic ratio applies more accurately than do other formulas

The other diameters especially the long and the broad are useful as supplements of the transverse but are more readily considered in connection with area measurements either made directly or by formula as in the nomogram in Figure 29

The measurement of the *area* of the heart shadow in the frontal silhouette

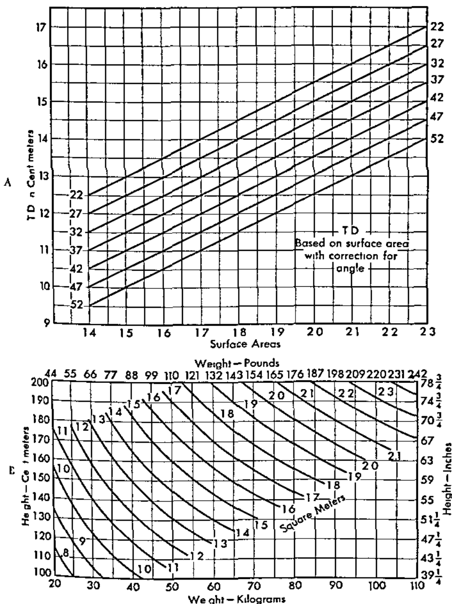


FIG 28 Corrections for angle of heart's axis (*A*) Chart for the determination of the normal variation of the measurement of the transverse diameter (T D) of the roentgen heart shadow with varying height and weight (Smith and Bloedorn *U S Naval M Bull* 19? XVI ?19)

(*B*) Chart for the determination of the surface area of the body from the height and weight (Dubois E F Fig 19 on page 119 of *Basal Metabolism in Health and Disease* 2nd ed Lea & Febiger Philadelphia 1927

that is on the usual anteroposterior teleroentgenogram or orthodiagram i theoretically sounder than that of the diameters and actually it has bee found to be fairly satisfactory when compared to the size of the individua as in the formula *orthodiagraphic cardiac area in sq cm = age × 0 0?04 + stature × 0 8668 + weight × 0 337 minus the constant 63 8049* (Hodges an

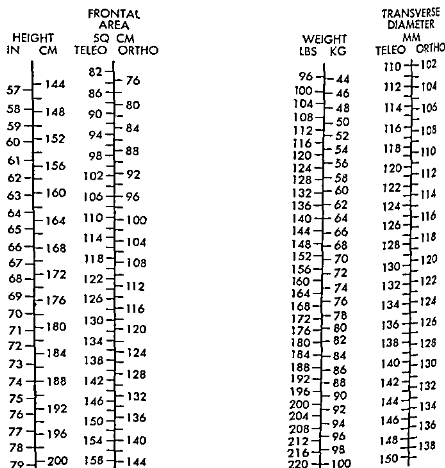


FIG 29A Nomograms for determination of the frontal area and transverse diameter of the normal heart shadow of teleroentgenogram and orthodiagram predicted from height and weight

The Hodges Eyster formula applied by Kurtz The roentgen films and orthodiagrams were made during quiet respiration Add 10 per cent of patient s age to predicted transverse diameter The measurement of the area by teleroentgenogram is 11 per cent greater than the area of the heart shadow by orthodiagram The transverse diameter of the heart shadow in the teleroentgenogram is 8 per cent greater than that of the orthodiagram

In making the determination a straight edge joins the figures for the height and weight of a given case The points of intersection of this line with those recording area and transverse diameter are then read off as representing the expected average area and with the addition of 10 per cent of the patient s age the expected average transverse diameter An allowance of 10 per cent extra is to be considered the extreme upper limit of normal (Kindness of Dr Chester M Kurtz Madison Wis)

Eyster 1924) Thus for a person fifty years old 173 cm (5 ft 8 in) tall and weighing 70 kg (154 lb) the orthodiagraphic cardiac area should be normally 112 sq cm If the heart area is found to be 7 sq cm larger than the predicted area by this formula the chances are 3 to 1 that the heart is actually enlarged if the actual area is 14 sq cm larger than the predicted area the chances of cardiac enlargement are 10 to 1 and if 21 sq cm larger the chances are 45 to 1 A simple calculation by slide rule or nomogram (Figure 29) can be made to determine the expected normal at any age height and weight for either orthodiagram or teleroentgenogram

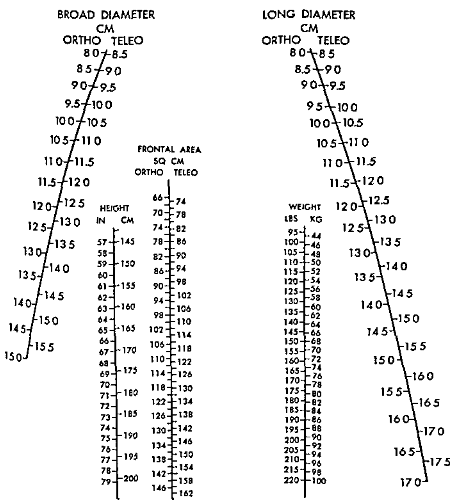


FIG 29B Area of heart shadow of orthodiagram and of teleroentgenogram determined from the long and broad diameters (the predicted area from height and weight) $A = \frac{\pi}{4} \times L \times B$ (Kindness of Dr Harry Ungerleider Equitable Life Assurance Society of the U.S New York City)

The ideal measurement of heart size by roentgen ray should be that of *volume* because of the established fact that the heart normally and abnormally varies considerably in all its diameters As yet however the determination of the heart volume has not been routinely introduced and under present conditions it is not likely that it can be satisfactorily applied clinically for two reasons (1) in the first place there is far too wide a range of normal heart size using recognized correlations and (2) the technic is not easy or accurate especially in the very cases of cardiac enlargement in which the physician is most interested Various formulas have been suggested especially those by Bardeen (1918) Kahlstorf (1932) Benedetti and Bollini (1934), and Strandquist (1935) Bardeen s formula is $0.53 \times A$ *(teleroentgenographic silhouette area)* $^{3/2} = V$ *(volume)* in a case with area of 100 sq cm the heart volume would be calculated to be 530 cc by this formula which is probably not far from the true volume of a partially filled heart in an adult of average size Kahlstorf's formula is V *(volume)* $= 0.63 \times$ *orthodiagraphic silhouette area of frontal plane heart shadow* $\times$ *maximum anteroposterior diameter* (D) If the area in a given case equals 100 sq cm and the anteroposterior diameter equal 8 5 cm the heart volume according to this formula would be 535 cc Benedetti and Bollini have published a formula for the tridimensional heart size Vc *(vol)* $= 0.45 \times$ *the long diameter of the heart in the anteroposterior orthodiagram* $\times$ *the broad diameter of the heart in the anteroposterior orthodiagram* $\times$ *the depth of the heart in the lateral orthodiagram* a case with long diameter of 12 cm transverse diameter of 10 5 cm and depth of 9 cm would thus have a volume of 510 cc Strandquist gives the following formula using orthodiagraphic measurements V *(volume)* $= 2/3 \times 1/2\ L$ *(long diameter)* $\times 1/2\ B$ *(broad diameter)* $\times S$ *(depth of heart in sagittal view)* using teleroentgenographic measurements he suggests $V = 0.42\ L \times B \times S$ Thus using the last named formula in the case of a normal adult with $L = 14$ $B = 10$ and $S = 9$ we find that $V = 529$ cc One must of course correlate the heart volume determined by any formula to body size and also to the degree of filling of the heart under some standard condition As has been noted already, the filling of the heart and hence its volume will vary greatly under certain conditions probably changing at least 100 per cent in passing from the Valsalva experiment to the Muller experiment (see page 135)

Careful clinical studies made at the Massachusetts General Hospital (Comeau and White, 1939 and 1942) have demonstrated the inadequacy of all these various measurements chiefly because of the wide range of the normal heart size and shape in connection with all recognized correlations such as height and weight and body surface area It is hoped that other standards representing types of body build may some day prove more suitable and permit more reliance on roentgen measurements At present the simple transverse diameter of the heart related to body height and weight following Hodges and Eyster s tables seems the most satisfactory measurement of heart size with area a moderately close second The reason why area is not better as it should be on first thought is that a considerable part (the upper and lower

borders) of the circumference of the heart shadow (in the anteroposterior view) has to be arbitrarily completed before the measurement by planimeter can be made This same reason plus the frequent difficulty of sharp measurement of the depth diameter of the heart (as well as the great range of normal) makes the volume calculation unsatisfactory The commonly used cardiothoracic ratio is in general too crude and its normal limits are far too wide however it can be useful in rare cases who are not tall but who have very wide chests

Finally it has been suggested that in addition to inspection of the size and density of the hilus shadows of the lungs in the anteroposterior heart shadow a measurement of their breadth be made This is much better done on the right side the measurement being actually that of the lower main branch of the right pulmonary artery Normally this hilus shadow measures 11 to 14 mm broad (average 13 mm) with the tube 1 5 meters away from thorax and screen If it is over 15 mm broad it is abnormal

Taken altogether these measurements of heart and aortic size should be interpreted very freely they are probably better than no measurements at all when they are so interpreted But when an attempt is made to fit each case within narrow so-called normal standard limits it is better to discard all measurements and to rely simply on general impressions and experience Some physicians do this now and are as successful in diagnosis as are other physicians who rely on extensive tables or formulas

Activity of the normal heart and great vessels as seen roentgenologically Normally the *atrial contractions* precede by a small fraction of a second (about 0 15 second) the contraction of the ventricles Theoretically this interval is sufficient to allow the atrial contractions to be visible in fluoroscopic examination but often this is not actually possible the vigorous ventricular action coming so soon after that of the atria that they both seem to share but a single motion If however the atria are enlarged and vigorous and very close attention is paid to the right atrial and left ventricular borders in the anteroposterior view or to the left atrial and left ventricular borders in the left anterior oblique view it is possible to distinguish a retraction of the atrial border ahead of the ventricular This separation becomes more and more obvious and marked with increasing delay in atrioventricular conduction and in complete block the atrial contractions may be clear Often atrial fibrillation weak or scant atrial contractions or obscure outlines prevent any evidence of atrial action at all in fluoroscopic examination and if there is free mitral or tricuspid regurgitation ventricular systole may be vigorous enough to cause an outward movement of the atrial borders

Ventricular action also varies very much normally in force extent and character In repose it tends to be quiet slight to moderate in fullness and slow with leisurely (that is relatively long) systole After exertion and with excitement it is active rapid and forceful with shorter systole with the special increase of circulation due to exertion the contractions are fuller as well as more rapid In the upright position a vertical heart may beat rapidly and force-

fully laboring to send out blood which is coming to it in too small an amount Firm abdominal pressure by relieving this situation slows and calms the heart action When the ventricles contract apex and base of the heart approach each other the base moving down in this process even more than the apex moves up and the heart rotates to the right so that the apex of the left ventricle strikes the chest wall This composite movement is more obvious in the case of the horizontally placed heart than in that of the vertical heart. It can be made more evident in either case by increasing the fullness of contraction by exercise The pulse of the ventricles is a single rapid process not accompanied by a wave of contraction the wave like change that is sometimes seen passing down over the base of the left ventricle with systole is simply the actual movement of the base that is the atrioventricular junction, toward the apex as the heart contracts

The *great arteries* that is the aorta and pulmonary artery are seen to dilate with systole as the blood is pumped into them this results in a vertical rocking or seesaw motion of the heart shadow with retraction below and outthrust above especially evident along the left border This motion can be increased by exercise or excitement and in itself is not abnormal except as it may be much magnified under certain conditions as for example with aortic or pulmonary regurgitation Pulsation of the great veins is not normally visible except for that of the superior vena cava in the recumbent position when atrial and ventricular waves are seen A slight pendulous movement of the heart is due to respiration and not to heart action itself Moderate pulsation of the lung hiluses due to the presence there of the larger branches of the pulmonary artery may be normally visible in thin adults or in children with increased heart action

Roentgenkymography electrokymography and roentgencinematography already described above are methods that may be employed to obtain permanent records of cardiac and vascular pulsation and thus to supplement fluoroscopy

ABNORMALITIES OF SIZE SHAPE AND ACTIVITY OF HEART AND GREAT VESSELS STUDIED BY ROENTGEN RAY

The various abnormalities of the roentgen shadows of the heart and great vessels will be presented in appropriate chapters later in the book with particular relation to etiologic types and structural defect The index may be consulted for quick reference to the special pages concerned A few further notes should be added however in concluding the present chapter

Disorders of cardiac rhythm Although it is possible to diagnose such disorders of mechanism as premature beats paroxysmal tachycardia atrial fibrillation and even flutter atrioventricular nodal rhythm and heart block by fluoroscopy their identification and analysis are so much easier and more complete by other methods of examination especially electrocardiography that fluoroscopy is not a procedure of choice for their study Their presence may be first noted in roentgen ray examination but details are sure to be missed

With tachycardia whether of physiologic or pathologic nature the heart shadow often decreases in size with bradycardia the reverse is usually true

Calcification Calcification may be noted in *heart arteries* or *pericardium* It is most commonly and easily seen in the peripheral arteries especially in those of the legs The tortuous course of the calcified vessels may be found with or without symptoms or signs of faulty circulation in muscles and skin such as intermittent claudication or gangrene The next most common site of visible calcification is the thoracic aorta the whole vessel may be clearly out lined by general calcification (Figure 144 page 749) or there may be irregu larities of density due to plaques The abdominal aorta may also be sufficiently calcified to be visualized by roentgen ray especially if there is much air in the overlying gastrointestinal tract Uncommonly there may be enough cal cification of a diseased pericardium to be visible by roentgen ray (see Figure 140 page 730) such calcification is best noted end on in the oblique or lateral views Sometimes calcified valves (especially in calcareous aortic stenosis) or areas in the myocardium (old infarcts) or even calcified mural thrombi may be seen Calcified coronary arteries may be recorded on the roentgenogram or seen fluoroscopically but only in cases of advanced disease which is usually clearly evident on clinical examination here the cal cification is simply a gravestone covering tissue long dead

Pressure on bones Changes of bones due to erosion or deformity caused by heart or blood vessels are to be looked for A very large heart in early childhood may cause a bowing out of the left anterior chest wall With coarcta tion of the aorta the ribs may be eroded by the widened intercostal arteries a result of the attempt of the body to compensate for this congenital defect (see Figure 77 page 332) in some cases the diagnosis of this congenital defect has been first suggested by roentgen ray examination Vertebrae ster num and ribs may be found to be eroded by the pressure from aneurysms of thoracic or abdominal aorta or of the main branches of the thoracic aorta

Fat shadows At the apex there is often a considerable triangle of fat lying in a fold between pericardium pleura and diaphragm (epipericardial fat) this is of less density than the heart shadow (see text and Figure 7 pages 38 and 39) and should not be confused with it to occasion an incorrect diagnosis of cardiac enlargement such as has frequently happened (McGinn and White 1936) This mass of fat may be as wide in transverse diameter as 2 cm it can be easily differentiated on fluoroscopy especially on deep inspiration and by contrast films There may be fat also at the right heart border but of lesser amount

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Ponsdomenech E R and Nunez V B "Heart Puncture in Man for Diodrast Visualization of the Ventricular Chambers and Great Arteries (I) Its Experimental and Anatomophysiological Basis and Its Technique and Heart Puncture (II) Cardioangiography Clinical and Electrocardiographic Results *Am Heart J* 1951 XLI, 643 and 855

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CHAPTER 8

THE PULSATION OF HEART AND BLOOD VESSELS SPHYGMOGRAPHY BALLISTOCARDIOGRAPHY THE CAPILLARY CIRCULATION

Very little revision of this chapter has been needed for the present edition of this book A brief section however has been added on ballistocardiography for it is here that such mechanical recording belongs

Harvey W *Exercitatio Anatomica De Motu Cordis Et Sanguinis In Animalibus* Frankfurt am Main 1628 (*An Anatomical Disquisition on the Motion of the Heart and Blood in Animals* Translation by Robert Willis for the Sydenham Society in 1847)

Chapter I The Author s Motives for Writing

"When I first gave my mind to vivisections as a means of discovering the motions and us s of the heart and sought to discover these from actual inspection and not from the writings of others I found the task so truly arduous so full of difficulties that I was almost tempted to think with Fracastorius that the motion of the heart was only to be comprehended by God For I could neither rightly perceive at first when the systole and when the diastole took place nor when and where dilatation and contraction occurred by reason of the rapidity of the motion which in many animals is accomplished in the twinkling of an eye coming and going like a flash of lightning so that the systole presented itself to me now from this point now from that the diastole the same and then everything was reversed the motions occurring, as it seemed variously and confusedly together My mind was therefore greatly unsettled nor did I know what I should myself conclude nor what believe from others I was not surprised that Andreas Laurentius should have said that the motion of the heart was as perplexing as the flux and reflux of Euripus had appeared to Aristotle

"At length and by using greater and daily diligence having frequent recourse to vivisections employing a variety of animals for the purpose and collating numerous observations I thought that I had attained to the truth that I should extricate myself and escape from this labyrinth and that I had discovered what I so much desired both the motion and the use of the heart and arteries since which

Williams F H "A Method for More Fully Determining the Outline of the Heart by Means of the Fluoroscope together with Other Uses of This Instrument in Medicine *Boston M and S J* 1896 CXXXV 335
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Rushmer R F "Cardiac Cinefluorography as a Training Method Abstract Program of 22nd Scientific Sessions Am Heart A 1949 p 44

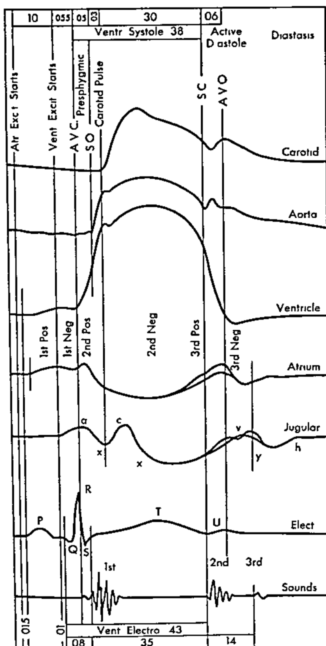


FIG 30 Chart showing time relations of electrocardiogram atrial and ventricular contractions pressure changes and heart sounds (Lewis *Mechanism and Graphic Registration of the Heart Beat* Kindness of Shaw and Sons Ltd London)

ence to the centre than in the opposite direction were there even no valves to oppose its motion

Sphygmography (σφυγμος pulse and γραφειν to write) is the process of obtaining a tracing of cardiovascular pulsation whether from the apex im pulse of the heart (*cardiogram*) from brachial radial or other artery (*arteri ogram*) from jugular or other vein (*phlebogram*) or from pulsating liver (*hepatogram*) The term polygram applies to simultaneous records of any two or more pulses or of pulse and respiration Commonly the polygram registers the brachial or radial pulse and the jugular pulse in addition the electrocardi ogram is usually recorded simultaneously or even replaces one of the other mechanical graphic tracings The instrument which makes any of these com bined tracings is called the polygraph The technic of sphygmography will not be discussed in this edition it is amply presented elsewhere (see Bibliography at end of this chapter) It need only be added here that developments in the last few years have made it possible to obtain with ease excellent electrical (galvanometric) tracings of cardiac arterial and venous pulses (Miller and White 1941) that total cardiac vibrations recorded by the cathode ray are now available for study (Kountz and Smith 1941) and that graphic records of the recoil of the body from the ejection of blood by the heart into the aorta (ballistocardiograms) have been utilized to estimate the cardiac output per beat (Starr et al 1939 1940)

CARDIOGRAM

Although it may seem at first thought that records of the pulsation of the heart itself transmitted to the chest wall should be simple and reliable evidence for the analysis of the mechanism of the heart beat experience has shown otherwise The result is that the cardiogram is rarely obtained or studied except in special instances or in investigative work The reasons for this neg lect are several In the first place the technic is often far from easy A thick chest wall pulmonary emphysema or very weak heart action may make it difficult or impossible to find any cardiac impulse at all In the second place the shape and interpretation of the tracing depend on what part of the impulse is recorded whether that over the left ventricle at the apex or that nearer the sternum over the right ventricle In the third place the complexity of the trac *ing which is often difficult to explain makes it less convenient than* the arteri ogram phlebogram and electrocardiogram in the analysis of arrhythmias And finally in our present state of knowledge at least more helpful informa tion is afforded us by the other tracings for example slight pulsus alternans in the arteriogram shown poorly or not at all in the cardiogram delay in atrio ventricular conduction in the jugular phlebogram found with difficulty by direct cardiography and information about the myocardium shown by intra ventricular block and T wave changes of the electrocardiogram and usually not even suggested by the cardiac apex tracing Nevertheless the cardiogram is of some individual interest for itself and should be briefly described

The normal cardiogram varies according to whether it is obtained over left ventricle or right ventricle (Figure 31) Over the left ventricle the outthrusts and hence the upstrokes of the tracing occur with systole over the right ventricle unless it is enlarged systole causes depression If the atrial contraction is vigorous and tracing conditions favorable we may find a definite upstroke a preceding the sharp higher ventricular upstroke of the left ventricular apex impulse or preceding in the same way the sharp ventricular downstroke over the right ventricle This a wave is more prominent over the right ventricle than over the left especially in the epigastrium A record taken where systolic outthrust and retraction merge will show various and sometimes confusing combinations of the two tracing shapes The wave due to ventricular contraction is usually overshot in the tracing partly because of the actual event but also because of the varying degrees of inertia of the apparatus employed Then follows during ventricular systole a settling down to a variable level till the shock of closure of aortic and pulmonary valves ends systole and begins diastole Quite early in diastole (about a tenth of a second after its onset) there may appear coincident with a protodiastolic heart sound a slight impulse due probably to the vibration of the ventricular walls from the current of blood that enters at that time (Figure 31) Such a diastolic event is more likely to be recorded with forceful slow heart action in thin young persons or with serious protodiastolic gallop rhythm (discussed in Chapter 5) Finally various oscillations may appear in the cardiogram which are unexplained but are probably due to vibrations of the chest wall

Abnormalities of the cardiogram include increased and decreased force and excursion of the atrial and ventricular systolic impulses and retractions delay between these impulses in heart block and extra waves in gallop rhythm (see Figure 31)

Gross pulsatory movements of the wall of the thorax resulting from the heartbeat (Dressler 1937) have already been referred to in Chapter 5 page 69

ARTERIOGRAM PULSE WAVE VELOCITY

Arteriogram An arterial pulse tracing may be obtained from almost any superficial artery but it is customary to use the brachial or radial artery for such a purpose Nearly a century ago the first attempts were made to study the circulation in man in health and disease by tracings on smoked paper made by crude instruments attached to the radial artery (Vierordt 1855 Marey 1860) Despite great expectations and extravagant interpretations the new records at first added little knowledge beyond that which had already been gained by mere palpation or inspection of the arterial pulse As a result sphygmography was abandoned for nearly half a century except for special studies The technic and apparatus poor and difficult at first slowly improved due to these special studies until with new discoveries concerning cardiac arrhythmia and alternation of the pulse the method was reintroduced into the clinic toward the end of the last century with far more success than at first

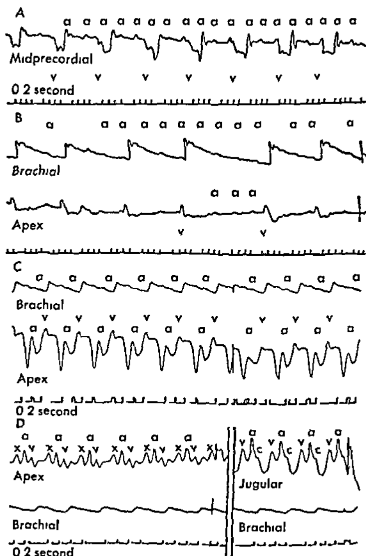


FIG 31 Cardiograms showing (*A*) ventricular systolic negative (v) and atrial systolic positive (a) waves in a case of complete heart block with the receiver placed over the precordium midway between the apex impulse and the lower end of the sternum and hence over the right ventricle (*B*) upstrokes with ventricular systole (v) and atrial systole (a) in the same case of complete heart block represented in (*A*) but with the receiver at the cardiac apex and hence over the left ventricle—note also the "a" waves in the brachial arteriogram taken simultaneously with the cardiogram (*C*) atrial (a) and ventricular (v) upstrokes with the receiver at the cardiac apex in a case with slight delay in a v conduction unusually vigorous atrial action and presystolic gallop rhythm and (*D*) three waves a v and x representing atrial ventricular and protodiastolic impulses with the receiver at the apex in a case of congestive failure showing well marked protodiastolic gallop rhythm without any delay in a v conduction (as proved by jugular phlebogram and electrocardiogram) Time interval = 0 2 second

It was almost entirely the shape and amplitude of the tracings that had attracted attention at the beginning rate and rhythm being largely ignored until many years later The various shapes of tracings of the arterial pulse were prominent in the textbooks of the day and it was hoped that they might prove more useful than they did We realize now that the shape and amplitude of the arteriogram are complicated not only in themselves but frequently also by the addition of artifacts due to the graphic method itself By the employment of more accurate apparatus the distortion can now be avoided

The normal arterial pulse wave The arteriogram consists of a graphic record of a series of pulse waves in an artery It should be of normal rhythm and rate (40 to 100 per minute at rest usually 60 to 80) The normal pulse wave (Figure 32) shows at first a sharp upstroke rising a variable distance from the baseline the amplitude depending on the fullness of the pulse and the sensitiveness of the recording apparatus Vibrations may be found on the upstroke if the curve is taken by the use of the Frank capsule crystal micro phone and galvanometer or cathode ray such vibrations are called anacrotic (ια up and κροτο stroke) The upstroke is quickly succeeded by a short sharp fall to a notch called the predicrotic (προ before δις second and κροτο stroke) resulting from the artifact of overshooting or fling due to instrumental inertia The distance from the peak of the wave to the predicrotic notch varies according to two factors the amount of inertia of the recording apparatus and the fullness of the pulse the more of each of these the greater the distance It is not always possible to make out this notch it may be buried in the rapid decline to the dicrotic notch especially where there is a water hammer or hyperdicrotic pulse shape Following the predicrotic notch appears the curved systolic decline ending as a rule abruptly at the dicrotic notch which repre sents the time of aortic valve closure and second heart sound The time interval from beginning of the main upstroke to the dicrotic notch (usually 0 25 to 0 35 second depending on the pulse rate) represents the duration of systole minus the so-called presphygmic (προ before and σφυγμος pulse) interval which is the time at the beginning of systole after the closure of the mitral and tricuspid valves (time of first sound) when intraventricular pressure is rising but not sufficiently to raise the aortic cusps and start the pulse wave along the aorta this presphygmic interval or isometric (σος equal and μετρον measure) phase is very short (calculated variously as 0 04 to 0 08 second) The dicrotic notch is followed by the dicrotic wave usually a slight convexity upward due to the rebound of the pulse wave at the closure of the aortic cusps This gives way to a gradual fall of the baseline to the next systolic upstroke Rarely a very small additional wave (a) occurs just preceding the systolic upstroke due to the effect of atrial systole on intraventricular and aortic pres sure Finally when more accurate tracings are obtained as already mentioned additional oscillations for example on the systolic upstroke may be seen doubtless due to vibrations of the artery wall their recording is not of any practical significance in the present state of our knowledge but may perhaps be found to be of some importance by future studies

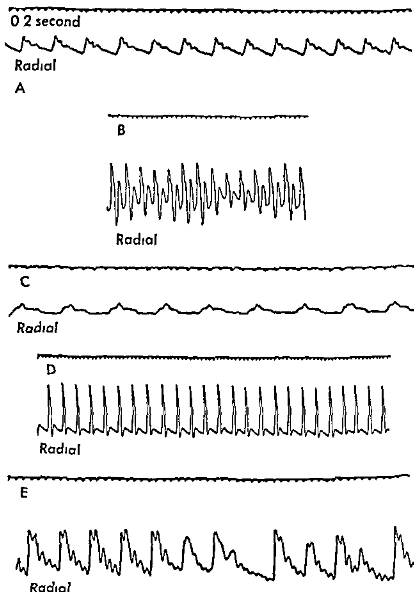


FIG 32 Arteriograms showing various shapes of pulse curves with normal rhythm (*A*) Normal average shape of arterial pulse wave showing upstroke predicrotic notch (due to artifact of overshooting from inertia of instrument) and dicrotic notch and wave (due to closure of aortic valve)—the duration of systole is equivalent to the interval from the beginning of the upstroke to the dicrotic notch plus a small time interval representing the presphygmic period (see text) (*B*) *Hyperdicrotic* pulse in infection showing exaggeration of the dicrotic notch and wave (*C*) Plateau and anacrotic pulse of aortic stenosis (*D*) Water hammer pulse of aortic regurgitation (*E*) Deformity of radial arteriogram due to oscillations caused by paralysis agitans Note also two ventricular premature beats Time interval of these and succeeding arteriograms and polygrams = 0 2 second

Abnormalities of the arterial pulse wave in shape and amplitude Slight changes in shape and amplitude of the arterial pulse wave from the average normal are so generally found in arteriograms or are so easily caused by the procedure of registration itself that only well marked variations such as can be palpated in the radial pulse should be considered here Great increase in pulse pressure that is true increase in artery fullness is not always easily apparent either on palpation of the arterial pulse or in the arteriogram Its detection is dependent on relative emptiness of the artery in diastole along with increase of pulse pressure but the diastolic laxness of the vessel is more essential than is increase in pulse pressure

Various abnormalities of shape and amplitude found in the arteriogram are illustrated in Figures 32 and 33

The most important by far of these abnormalities is *pulsus alternans* which consists of alternating fullness of pulse and of systolic and pulse pressure during normal heart rhythm the result of weakness (generally serious) of the left ventricle (see Chapter 30) An interesting variation abnormal and diagnostic (usually of acute or chronic constrictive pericarditis) when of high degree is the *pulsus paradoxus* which consists of waxing and waning of the pulse volume (and pressure) with expiration and inspiration respectively in contrast to the usual increase of the pulse fullness during inspiration and its decrease during expiration in the case of normal diaphragmatic breathing in marked instances the radial pulse may entirely disappear during inspiration (see Chapters 6 and 27) The various arrhythmias will not be illustrated here because they are so much better shown in electrocardiograms (see Chapters 32 33 and 34)

Velocity of the arterial pulse wave Quite aside from form and rhythm of the pulse and speed and volume of blood flow is the measurement of the velocity of the arterial pulse wave This has been estimated in various ways most simply by measuring the time interval between the appearances of the carotid and radial pulse waves graphically recorded simultaneously and dividing this time interval into the difference in centimeters between the distances from the heart of the recording points on the two arteries This gives roughly the speed of travel of the pulse wave in centimeters per second More accurate methods for making this measurement have been in recent years introduced such as that of the use of the hot wire sphygmograph which is an instrument transforming into variations of an electric current recorded by galvanometer the air pressure waves transmitted from a pulsating vessel or from the heart through a tube past a fine spiral of platinum wire heated by the electric current whose variations are recorded the ends of this wire being connected with the galvanometer Normally the pulse wave velocity in the brachial and radial arteries has been found to be 5 to 9 meters per second averaging about 7 meters It is increased in hypertension and arteriosclerosis and decreased in hypotension aortic stenosis and aortic aneurysm It varies roughly with the speed of blood flow but it has little or no relation

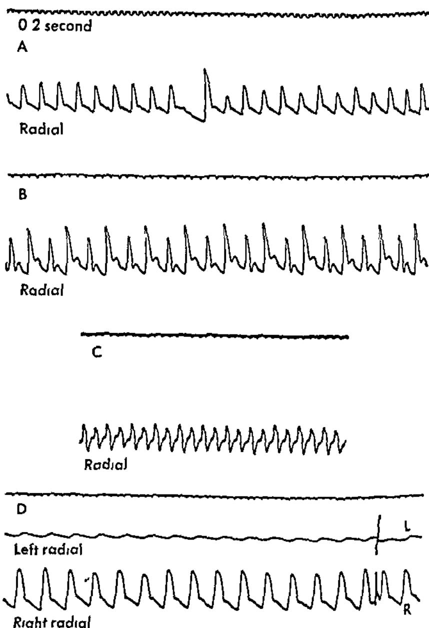


FIG 33 Arteriograms showing pulsus alternans and unilateral pulse deformity due to aneurysmal obstruction (*A*) Ventricular premature beat with compensatory pause followed by slight to moderate alternation of the pulse (*B*) Constant pulsus alternans showing delay in appearance of alternate weak beats (*C*) Pulsus alternans during a paroxysm of tachycardia (rate 185 per minute) (*D*) Diminished and delayed left radial pulse waves due to aortic aneurysm with obstruction at the mouth of the left subclavian artery

to volume of blood flow The measurement of the velocity of the pulse wave is not of much clinical value

PHLEBOGRAM HEPATOGRAM

Phlebogram (φλεψ vein and γράμμα inscription) The phlebogram or graphic record of the venous pulse is routinely obtained from the jugular vein Although on rare occasions pulsations may be easily visible in other superficial veins as in the arms the jugulars as a rule are the only veins that show enough pulsation to give a satisfactory record this is due to their large size and close proximity to the heart Venous pulsation has been known for centuries but it was not until the latter half of the last century that the development of the sphygmograph permitted the taking of actual tracings (Friedreich 1866 Potain 1867) and serious study of these venous pulse tracings did not begin until stimulated by a curiosity concerning the clinical significance of variations of this pulse (Mackenzie 1893) Gradually by comparing the phlebogram thus obtained with cardiac or arterial pulse tracings it became possible to recognize although not completely to explain the various waves of the normal jugular pulse and to describe certain abnormalities

In the clinic for a while the analysis of disturbances of the cardiac mechanism like partial heart block was chiefly dependent on the study of the polygram which consisted of simultaneous jugular and arterial pulse tracings But the frequently difficult and bothersome technic and the obscurity concerning interpretation in the minds of most physicians prevented a wide adoption of the method doctors remaining content to continue for years the old custom of labeling irregularity of the heart rhythm as slight moderate or marked Eventually the interest of younger workers and especially the introduction of the practical electrocardiograph the string galvanometer into the field of internal medicine resulted in the clinical applications of the lessons about cardiac mechanism first studied in the phlebogram by pioneers The electrocardiogram gives information about the cardiac mechanism which is so much more accurate and complete than that given by the phlebogram and the technic of securing the electrocardiogram and its interpretation when obtained are both so much easier that the phlebogram has been almost completely abandoned However as in the case of the arteriogram help can still sometimes come from the phlebogram To represent graphically what one can see of jugular pulsation aids in understanding the mechanical evidences of cardiac action and is good training Also in certain cases when the electrocardiograph is not available and one deals with arrhythmias difficult to analyze without knowing how the atria are acting the phlebogram may solve the problem And even when an electrocardiogram has been secured the question as to whether atrial waves are isoelectric or buried in ventricular waves may be answered by a study of the phlebogram The jugular pulse tracing gives something the electrocardiogram cannot give that is mechani

cal evidence of action of the heart chambers moreover certain abnormalities of the jugular pulsation may reveal cardiac insufficiency even when the electrocardiogram is normal In addition one can by electrical recording now obtain phlebog ams with greater ease and accuracy than was possible in the past (Miller and White 1941)

The normal and abnormal jugular phlebogram Although proof does not exist for every detail of the interpretation of the normal jugular pulse tracing the phlebogram is understood sufficiently to permit fairly full analysis With each cardiac cycle there are normally three four five or even six waves in the jugular pulse Interpretation by inspection of these waves especially if there are more than three may prove to be very confusing Therefore although it is at times possible to see and to identify the three normal waves or in the case of abnormalities to make correct analyses there are so many variations that in spite of much experience interpretation by inspection of the vein is far less reliable than interpretation of the phlebogram itself

There are three main waves in the jugular pulse (Figure 34)

The first wave due to atrial systole, has been routinely called the *a* wave It can be identified only indirectly after the other two main waves (which are of ventricular origin) have been accurately measured off as a rule it precedes the second or *c* (ventricular systolic) wave by one fifth of a second and it is variable in size depending chiefly on the posture of the subject the force of the atrial contraction and the degree of dilatation of the jugular vein Other factors which influence the size of the *a* wave normally are instrumental technic and the fullness of blood flow With poor technic for example by the application of too much pressure so that the vein is nearly collapsed or by holding the receiver somewhat away from the optimum position the *a* wave of the phlebogram may be small and poorly defined With increased heart action the *a* usually increases in amplitude and with increased circulation associated with increased blood volume such as may temporarily result from the ingestion of a large amount of fluid the *a* wave may also increase in size It is biggest of all in cases of marked tricuspid stenosis with normal rhythm It is ordinarily a single wave a rounded upstroke rising sometimes at the peak of the jugular pulse sometimes low near the baseline and sometimes at midlevel its position depending on the speed of the pulse on the degree of stasis in the vein and on the relative submergence of the *a* in the ventricular systolic wave The slower the pulse or the more congested the vein the more the *a* wave tends to appear at the top of the curve The faster the pulse the less the congestion and especially the more the systole of the ventricles is emphasized in the tracing the lower lies the *a* wave Although the *a* wave appears normally to be a single wave this appearance may be in part due to the immediate succession of the ventricular systolic wave which conceals any other portion of the *a* wave When there is a delay in atrioventricular conduction partial or complete sufficient to separate clearly atrial and ventricular waves the *a* wave sometimes appears doubled

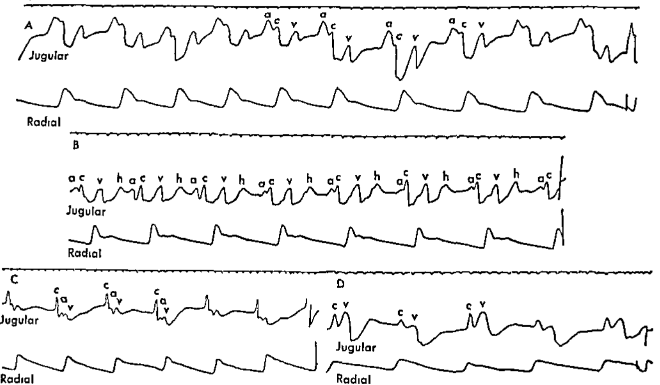


FIG 34 Polygrams showing the jugular phlebogram in (*A*) normal sinus arrhythmia (*a* = atrial *c* = ventricular and *v* = stasis waves) (*B*) sinoatrial bradycardia with *h* waves (see text) in addition to the *a* *c* and *v* waves (*C*) atrioventricular nodal rhythm in which the atrial contraction follows the ventricular as shown by the interpolation of the *a* wave between the *c* and *v* waves and (*D*) atrial standstill in which condition no *a* waves are seen either between or with the regularly recurring *c* and *v* waves

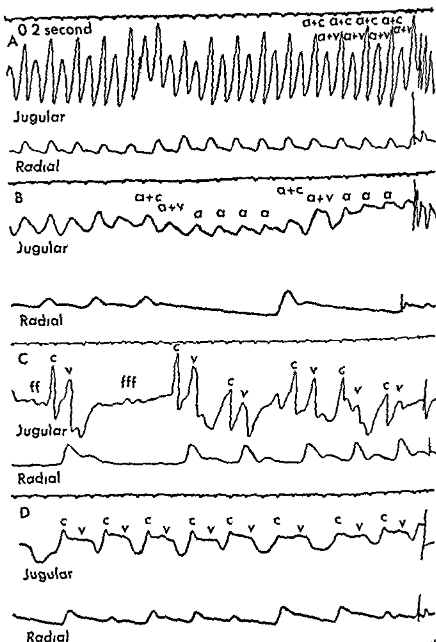


FIG 35 Polygrams showing the jugular phlebogram in (*A*) atrial flutter with two to one a v block (*a* = atrial c = ventricular and v = stasis waves) (*B*) atrial flutter with varying and higher degrees of block the *a* waves being clearly evident between the c waves (*C*) atrial fibrillation with no *a* waves but with oscillations (fff) due to the irregular atrial contractions and (*D*) atrial fibrillation with the so-called "ventricular" or better designated "congestive" type of venous pulse due to coalescence of *c* and v waves resulting from stasis

or at least notched (Figure 36) Various abnormalities of the jugular phlebo gram are illustrated in Figures 34 35 and 36 Arrhythmias are not presented because of their better analysis by electrocardiography (Chapters 32 33 and 34) except as they illustrate particular points concerning the venous pulse tracing

The a-c interval The atrial wave of the jugular pulse tracing precedes normally that due to ventricular systole by 0 15 to 0 20 second if there is a greater time interval (measured from the beginning of the *a* upstroke to the beginning of the *c* upstroke) atrioventricular block is present

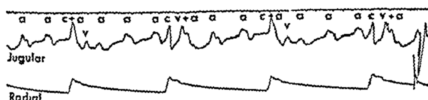


FIG 36 Polygram showing the jugular phlebogram in complete atrioventricular block with complete dissociation of *a* and *c* waves Note bifid *a* waves Size reduced

Following the first or *a* wave of the normal jugular phlebogram by the time interval just noted above appears the second or *c* wave which is due to ventricular systole It was labeled *c* because it was attributed to the pulsation of the carotid artery lying under the jugular vein Undoubtedly the carotid pulsation does play an important part in its production but this part is variable in degree In the venous pulsation itself there is a ventricular systolic wave transmitted up from the right atrium by way of the superior vena cava This wave together with that due to the carotid pulsation forms the upstroke *c* of the jugular phlebogram a positive wave of varying amplitude whose size depends upon a number of factors The greater the carotid element of the *c* wave the higher and more preponderant is this wave and vice versa There is one type of patient with mitral stenosis with greatly exaggerated *c* (and *v*) waves of the jugular pulse itself that deserves special mention This pulsa tion concerns the deep jugular veins on both sides of the neck but especially the right one Because as a rule atrial fibrillation is present in these patients with no *a* waves in the phlebogram because the pulse is so vigorous and because it is so deep in position in the neck it is easily and commonly confused with the carotid pulse (White and Cooke 1939) It is due to tricuspid re gurgitation with relatively little constant congestion or stasis so that the pulse wave is propelled vigorously by right ventricular systole through tri cuspid valve right atrium and superior vena cava into the jugular veins it is easily obliterated by slight pressure over the jugular bulb As a rule tricuspid valve deformity with stenosis is present in these cases of such pulsation of long standing but in rare instances there is chronic irreversible dilatation of the tricuspid ring without valve deformity

The *c* wave itself is identified by comparative measurement from the up stroke of the pulse wave of the brachial or radial arteriogram or of the *QRS*

wave of the electrocardiogram which is taken simultaneously with the jugular phlebogram for this very purpose Measuring back from simultaneous time lines of both tracings established by allowing the pens each to write a stroke with the recording surface at rest the beginning of the upstroke of the *c* wave will be found one tenth of a second earlier than the upstroke of the radial pulse wave or 0 135 second later than the *QRS* wave this difference in time being that interval required for the pulse wave to travel a length of artery equivalent to the difference between the distances of the radial pulse and of the jugular pulse from the heart in the first instance and to the sum of the travel time from the heart to the jugular bulb and of the electrical pre sphygmic interval in the second instance (see Figure 31 page 158)

The *c* wave may be found to occur irregularly rapidly or slowly and to be of varying shapes and amplitudes but these characteristics of the arterial pulse and of heart action are better studied in the arteriogram itself as already discussed or in the electrocardiogram

The third main wave the *v* wave of the jugular phlebogram is due pri marily to stasis that is to the gradual accumulation of blood in right atrium superior vena cava and jugular bulb at the close of ventricular systole This stasis ends rather abruptly in a rounded peak and downstroke when diastole begins and the blood flows down into the right ventricle from atrium vena cava and jugular bulb It has been called routinely the *v* wave for ventricular systole but a more correct expression might have been *s* for stasis while the *c* wave might better have been called the *v* wave However the firm stablish ment and the partial correctness of these designations warrant their retention. A second factor besides stasis which has been suggested as in part responsible for the *v* wave is the rebound or return upward of the base of the heart at the beginning of diastole We do not know the relative importance of the two elements (the rebound and the stasis) or whether the frequent splitting of the *v* wave which is unexplained can result from their difference in time (the diastolic rebound effect being later than the other) but evidence strongly sup ports the conclusion that stasis and not diastolic rebound is the essential cause of the *v* wave The amplitude of the *v* wave varies as does that of the *a* wave and as a rule inversely as that of the *c* wave It is dependent to an im portant degree on the amount of venous stasis If there is much stasis the *v* wave is more prominent if the stasis is extreme in degree there appears a characteristic variation consisting in a merging of *c* and *v* waves in one broad plateau with slight elevations at the ends and variable concavity between (Fig ure 35) This type of jugular pulse was once called the ventricular type apparently because it was so often found in atrial fibrillation with absence of *a* waves But it may be found with normal rhythm and *a* waves It is due to congestion and so it may better be called the congestive type of jugular pulse

The *v* wave is determined in its position in the jugular phlebogram by correlation with the radial arteriogram simultaneously recorded Measuring back from synchronous points we find that the dicrotic notch of the arterial

pulse coincides with the peak of the v wave though sometimes it may fall between the two peaks of the v Actually the dicrotic notch of the radial pulse represents closure of the aortic valve an earlier event by 0 05 to 0 1 second than the opening of the tricuspid valve which is responsible for the beginning of the downstroke of the v wave But since the pulse wave takes almost 0 1 second longer to reach the wrist (or slightly less time to reach the elbow) than to reach the base of the neck these two events can be measured off together in the polygram

One further wave may be found infrequently in the jugular pulse tracing especially with slow forceful heart action It is a small wave in diastole called the *h* or *b* wave (Hirschfelder 1907 Gibson 1907) It is related to the pre ceding ventricular systole and not to the succeeding *a* or *c* waves which it may closely approach in time if the pulse is fast It has been ascribed to the same mechanism that produces the normal third sound of the heart or the ab normal extra sound in protodiastolic gallop rhythm but its timing sometimes appears late for this It is not well understood further study is needed to explain it Whatever its mechanism it does not at present appear important except that its existence should be recognized so that it will not be confused with other waves (Figure 34) The *a* and *h* waves are located by a process of exclusion after the *c* and v waves have been identified

What has been termed a second stasis or second onflow wave is the gradual movement upward of the baseline of the jugular phlebogram late in diastole just prior to the *a* wave it is prominent if there is bradycardia or congestion

An interesting phenomenon which sometimes interferes with smooth record ing of the jugular pulse is the paradoxical inspiratory filling in cases of venous hypertension (Hitzig 1942) this has been discussed in Chapter 6 page 120 It emphasizes the need well known to those experienced in phlebography to obtain for their smoothness records taken during held respiration that is held in whatever phase brings out the pulse waves to the best advantage

An esophageal tracing of the left atrial pressure changes (esophagocardio-gram) shows three waves usually corresponding to the *a* *c* and stasis waves of the jugular pulse tracing the *a* and *c* waves may be inverted if the receiver (a capsule filled with air) lies directly over the left atrium for the atrium recedes when it contracts as does the left ventricle This method however is an impracticable and unnecessary one

Hepatogram (ηπαρ liver and γραμμα inscription) A brief discussion of the liver pulse remains A true perceptible liver pulse not due to directly transmitted systolic movement of the liver by heart aorta or aneurysm is uncommon The reason for this is that the liver is so sponge like that it absorbs much blood and much pulsation before it becomes sufficiently in-fluenced actually to cause a visible palpable or traceable pulse Slowly pro gressive *chronic pericarditis or heart failure although resulting in much* hepatic enlargement with some fibrotic change and ascites does not cause liver pulsation Three factors are responsible for this pulsation (1) rapid acute congestion with failure and functional tricuspid regurgitation (2)

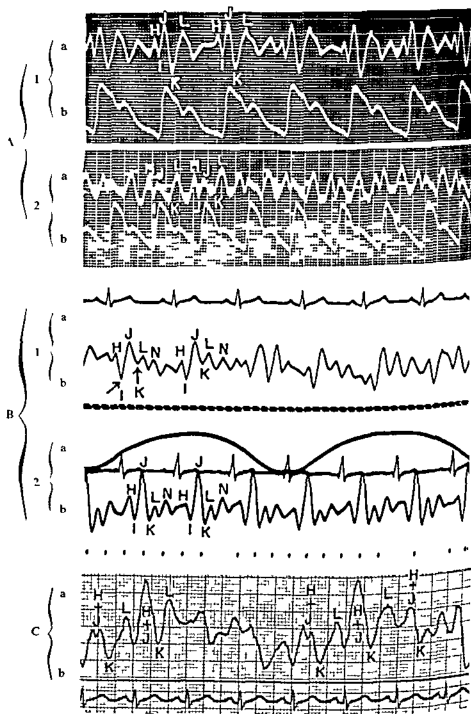


FIG 38 Ballistocardiograms (*A* 1) Normal curve Male age 34 Tracing shows normal waves H to K (period of cardiac ejection) Amplitude of J and K roughly approximate clinical measure of the stroke volume of the heart (*a* ballistocardiogram *b* arteriogram) (*A* 2) During acute rheumatic carditis The J and K waves are of

Rheocardiogram The changes that occur in the body s electrical resistance with each heartbeat can also be recorded electrically by connecting electrodes on right arm and left leg to alternating current of high frequency (10 000 to 50 000 oscillations per second) Measurement of electrical impedance of the body is not new in 1937 Mann stated When the electrical conductivity of any part of the body is measured by means of an alternating current bridge it is found that this conductivity shows a rhythmic variation synchronous with the pulse The curve which has been called an electrical plethysmogram ascends with increase in body resistance during systole when the heart volume decreases relative to the lung air volumes on either side and descends when diastole begins In myocardial failure with prolongation of the isometric period the descent of the curve is delayed and with mitral regurgitation the ascent is slowed (Holzer and Polzer 1947) Complete inversion of the curves has been reported in cases with extensive edema with reversal when the edema cleared (Weissel 1948) This technic has not however been adopted routinely in clinical practice further investigation is needed even to determine whether or not it has any value as a research tool Recent work has indicated its possible value in the study of the peripheral circulation (Nyboer 1950) where it may act as an electrically recording plethysmograph

CAPILLARY CIRCULATION AND PULSATION

It remained for Malpighi in 1661 to complete the proof of the circulation of the blood presented by Harvey in 1628 Harvey had postulated that "in the limbs and extreme parts of the body the blood passes either immediately by anastomosis from the arteries into the veins or mediately by the pores of the flesh, or in both ways as has already been said in speaking of the passage of the blood through the lungs Only in recent years has the existence of direct anastomoses between arteries and veins been demonstrated (Grant, 1931 Grant and Bland 1931) but the pores of the flesh or capillaries were discovered in the lungs by Malpighi.

Malpighi in a letter to Professor Alphonsus Borellius of Pisa describes his discovery of the pulmonary capillaries. (*De pulmonibus observationes anatomicae* Bologna 1661 translated by James Young M D *Proc Roy Soc Med* 1929–1930 XXIII 7–11 Part I)

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low amplitude with relatively tall H and L waves (*a* ballistocardiogram *b* arteriogram) (Kindness of Dr William Dock Brooklyn, N Y)

(*B* 1) Ballistocardiogram and electrocardiogram of case of coarctation of aorta before operation showing relatively small J wave and very small K wave The arrows point to the short J and K strokes characteristic of coarctation of the aorta (*a* electrocardiogram *b* ballistocardiogram) (*B* 2) Same case after operation the J and K waves are now normal (*a* electrocardiogram *b* ballistocardiogram) (Kindness of Dr Herbert R Brown, Jr., Rochester N Y., and *New England J Med*)

(*C*) Case of angina pectoris, A D male age 49 Note respiratory effects but in particular the fusion and/or notching of the H and J waves (*a* ballistocardiogram *b* electrocardiogram) (Kindness of Dr William Dock, Brooklyn, N Y)

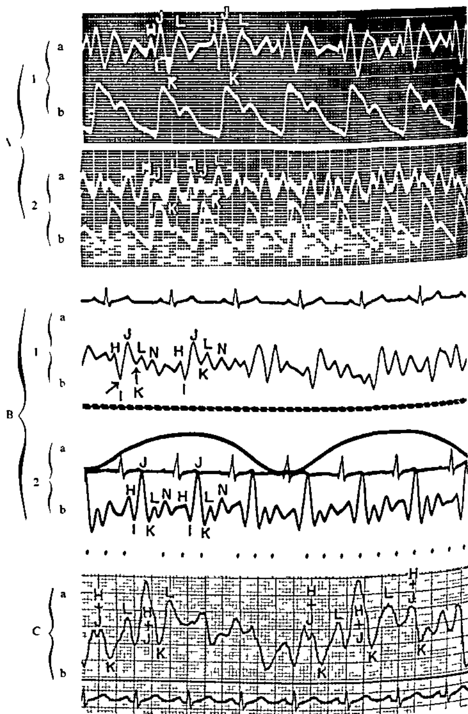


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(C) Case of angina pectoris A D male age 49 Note respiratory effects but in particular the fusion and/or notching of the H and J waves (*a* ballistocardiogram *b* electrocardiogram) (Kindness of Dr William Dock Brooklyn N Y)

And now most famous man I will handle the matter more closely There were two things which in my epistle about observation on the lungs I left as doubtful and to be investigated with more exact study

(1) The first was what may be the network described therein where certain bladders and sinuses are bound together in a certain way in the lungs

(2) The other was whether the vessels of the lungs are connected by mutual anastomosis or gape into the common substance of the lungs and sinuses

The solution of these problems may prepare the way for greater things and will place the operations of Nature more clearly before the eyes For the unloosing of these knots I have destroyed almost the whole race of frogs which does not happen in that savage Batrachomyomachia of Homer For in the anatomy of frogs which by favour of my very excellent colleague D Carolo Fracassato I had set on foot in order to become more certain about the membranous substance of the lungs it happened to me to see such things that not undeservedly I can better make use of that (saying) of Homer for the present matter—

I see with my eyes a work trusty and great

For in this (frog anatomy) owing to the simplicity of the structure and the almost complete transparency of the vessels which admits the eye into the interior things are more clearly shown so that they will bring the light to other more obscure matters ——

Observation by means of the microscope will reveal more wonderful things than those viewed in regard to mere structure and connection for while the heart is still beating the contrary (i e in opposite directions in the different vessels) movement of the blood is observed in the vessels —though with difficulty—so that the circulation of the blood is clearly exposed This is more clearly recognized in the mesentery and in the other greater veins contained in the abdomen

Thus by this impulse the blood is driven in very small (streams) through the arteries like a flood into the several cells one or other branch clearly passing through or ending there Thus the blood much divided puts off its red colour and carried round in a winding way is poured out on all sides till at length it may reach the walls the angles and the absorbing branches of the veins

The power of the eye could not be extended further in the opened living animal hence I had believed that this body of the blood breaks into the empty space and is collected again by a gaping vessel and by the structure of the walls The tortuous and diffused motion of the blood in divers directions and its union at a determinate place offered a handle to this But the dried lung of the frog made my belief dubious This lung had by chance preserved the redness of the blood in (what afterwards proved to be) the smallest vessels where by means of a more perfect lens no more there met the eye the points forming the skin called Sagrino but vessels mingled annularly And so great is the divarication of these vessels as they go out here from a vein there from an artery that order is no longer preserved but a network appears made up of the prolongations of both vessels This network occupies not only the whole floor but extends also to the walls and is attached to the outgoing vessel as I could see with greater difficulty but more abundantly in the oblong lung of a tortoise which is similarly membranous and transparent Here it was clear to sense that the blood flows away through the tortuous vessels that it is not poured into spaces but always works through tubules and is dispersed by the multiplex winding of the vessels ——

Physiologic studies of the capillary circulation have in late years attracted much attention and have revealed new facts of some importance (Krogh Lewis Lombard Richards Crawford Landis) but in routine or even in special cardiovascular examination they have not yet proved important The reasons for this are two In the first place but few capillaries in man can be studied and these are at the body surface best seen at certain localities like the nail beds and subconjunctiva (and with difficulty in the eye grounds) In the second place great variations of capillary conditions exist not only throughout the body at a given moment but even in a single area at different moments due to the frequent periods of changing activity (dilatation) and rest (contraction) characteristic of arterioles and body capillaries in general Thus capillary findings at a given moment in a given area may be very different from those in many other areas or in the same area at a different time There are however certain clinical facts of interest determined by scrutiny of skin capillaries by microscope through the intervention of oil and the use of reflected light for illumination (Lombard 1912) In cyanotic states as in some cases of congenital heart disease with polycythemia or in one of the phases of Raynaud s disease capillaries of the fingers are widely dilated while the blood stream through them may be sluggish normal or rapid according to the state of the arterioles In conditions of pallor as in another phase of Raynaud s disease the capillaries and arterioles are constricted and the blood stream is slowed The ingenious studies by Crawford (1926 1927) and Landis (1930 1934 1938) have revealed interesting facts about the structure and action of the capillaries and concerning capillary blood pressure and permeability

Capillary pressure Landis (1930 1934 1938) by microinjection measured directly and studied the mean blood pressure in the capillaries of the human skin at the base of the finger nail He found the average pressure in the arteriolar limb of the capillary to be 32 mm of mercury at the end of the loop 20 mm and in the venous limb 12 mm The fall of blood pressure does not cease at the junction of the arterioles and capillaries he wrote but continues unbroken through the capillary loop Average blood pressure in the arteriolar limb is above and in the venous limb below the osmotic pressure of the plasma proteins These direct pressure readings in human capillaries are in agreement with Starling s hypothesis of fluid balance Landis further found that hyperemia due to heat was attended by a doubling of the capillary blood pressure Eichna and his associates (1942 1943) have shown that despite the fact that pressure in the capillaries of the digits falls somewhat with arteriolar constriction and rises somewhat with increase in venous pressure there is a surprising degree of constancy in the digital capillary pressure during wide fluctuations in digital blood flow Eichna (1943) reported his finding of the average digital capillary blood pressure in human fingers with intact innervation to be 18 5 mm of mercury in the arteriolar limb (summit 22 4) and 19 mm in the venous limb Recently Pappenheimer and Soto

Rivera (1948) have further confirmed the concept that capillary pressure and colloid osmotic pressure are in balance by measuring the rate of filtration of fluid from blood to tissues and absorption of fluid from tissues to blood in the isolated hindlimbs of cats and dogs under conditions such that the arterial perfusion pressure the venous pressure and the protein osmotic pressure could be independently adjusted to desired constant values

Capillary pulsation Capillary pulsation can be recorded only photographically by cinematograph under high power magnification With low power magnification pulsation in the smaller arteries would be predominant Visible capillary pulsation is due to vasodilatation or marked aortic regurgitation allowing the arterial pulse to enter the capillaries without adequate damping The site of the color change is in the subpapillary venous plexus (Lewis 1927) This capillary or venular pulsation may be general throughout the body or very local

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CHAPTER 9

ELECTROCARDIOGRAPHY

One of the interesting medical achievements of our time has been the rapid indeed one might say dramatic growth of electrocardiography (ηλεκτρον amber friction of which gives rise to an electrical charge καρδια heart and γραφειν to write) To those of us who received our initial training in this field in the early days of clinical electrocardiography this evolution has been both gratifying and impressive not to say at times confusing The confusion has been due to two factors first the absence at the beginning of an adequate application of fundamental physical laws and principles so that the early growth was more empirical than scientific and second the lack of uniform technic and nomenclature utilized by various workers in the field This vigorous independence of thought and action has however its good side and agreement about utilization of the most satisfactory viewpoints and criteria will naturally follow We are still in the very midst of considerable new research and development in electrocardiography It would be impossible for me in the limited space available in this new edition to expand the chapter sufficiently to present the subject in all of its current detail I shall retain the story of the evolution of clinical electrocardiography with a brief survey of its present status and refer the reader for a more complete description of technic debatable theories and current research to the numerous monographs now available and listed in the Bibliography at the end of the chapter

Electrocardiography is one of the most important methods of cardiovascular examination ranking in value third after history taking and physical examination Like cardiovascular roentgenology it has continued to develop rapidly as the result of concentrated study in the past decades

Near the end of the eighteenth century Galvani and Volta and their followers began their important studies on electricity by utilizing that produced by animals Galvani for example in 1791 used the electrical organ of the torpedo-fish to stimulate not only the muscles and nerves of the frog but also the heart itself

About the middle of the last century it was learned in the exp

laboratory that when the pigeon s or the frog s heart contracted it produced an electric current (Matteucci 1843 Kolliker and Muller 1856) For many years after this discovery the heart current of laboratory animals was studied with the crude apparatus at that time available

Matteucci Ch Sur le courant électrique des muscles des animaux vivants ou recemment tues *Comptes Rendus des Seances de l Academie des Sciences* 1843 XVI 197

1 The signs of the electrical current of the frog itself demonstrated by the galvanometer increase in the same instrument in the act of contraction

2 *The muscular electrical current* which I shall hereafter call the muscular current is present in all muscle masses whatever the animal

I have taken pectoral muscles of pigeons a rabbit s back muscles hearts of pigeons In all cases I have obtained a current which flows from the interior of the muscle to the surface (Translation by myself)

Kolliker A and Muller H Nachweis der negativen Schwankung des Muskel stroms am naturlich sich contrahirenden Muskel *Verhandlungen der phy sicalisch medicinischen Gesellschaft in Wurzburg* 1856 VI 528

The results which up to now we have obtained from the frog s heart are as follows

1 The apex of the whole heart is electrically negative to any point on the anterior or posterior surface of the ventricles

2 Similarly negative is the apex of the heart to the cut surfaces left after removing the auricles without injury to the ventricles

3 On the other hand the cardiac apex is positive to any cross section which involves the ventricular musculature itself

4 Every point on the surface of the heart is positive to any selected cross section of the ventricle

5 The excursion given by connecting the outer surfaces of the base and of the apex of the heart is less than that given by connecting the cross section of the apex and the surface (Translation by myself)

Then came the discovery six decades ago also in the physiologic laboratory that the human heart current could be demonstrated by connecting the outside of the body by electrodes with the capillary electrometer (Waller 1887)

Waller A D A Demonstration on Man of Electromotive Changes Accompanying the Heart s Beat *J Physiol* 1887 VIII 229

If a pair of electrodes (zinc covered by chamois leather and moistened with brine) are strapped to the front and back of the chest and connected with a Lippmann s capillary electrometer the mercury in the latter will be seen to move slightly but sharply at each beat of the heart If the movements of the column of mercury are photographed on a travelling plate simultaneously with those of an ordinary cardiographic lever a record is obtained as under (fig 1) in which the upper line h h indicates the heart s movements and the lower line l l the level of the mercury in the capillary Each beat of the heart is seen to be accompanied by an electrical variation [This very first published electrocardiogram is essentially

the chest lead reintroduced as Lead 4 into clinical electrocardiography in recent years]

The first and chief point to determine is whether or no the electrical variation is physiological and not due to mechanical alteration of contact between the electrodes and the chest wall caused by the heart s impulse To ascertain this point accurate time measurements are necessary a physiological variation should precede the movement of the heart while this could not be the case if the variation were due to altered contact Fig 2 is an instance of such time measurements taken at as high a speed of the travelling surface as may be used without rendering the initial points of the curves too indeterminate It shows that the electrical phenomenon begins a little before the cardiographic lever begins to rise

That a true electrical variation of the human heart is demonstrable may further be proved beyond doubt by leading off from the body otherwise than from the chest wall If the two hands or one hand and one foot be plunged into two dishes of salt solution connected with the two sides of the electrometer the column of mercury will be seen to move at each beat of the heart though less than when the electrodes are strapped to the chest The hand and foot act in this case as leading off electrodes from the heart and by taking simultaneous records of these movements of the mercury and of the movements of the heart it is seen that the former correspond with the latter slightly preceding them and not succeeding them as would be the case if they depended upon pulsation in the hand or foot This is unquestionable proof that the variation is physiological for there is here no possibility of altered contact at the chest wall and any mechanical alteration by arterial pulsation could only produce an effect 0 15" to 0 20 after the cardiac impulse A similar result is obtained if an electrode be placed in the mouth while one of the extremities serves as the other leading off electrode The electrical variation precedes the heart s beat as in the other cases mentioned

The mercury column moved up and down several times with each heartbeat but the records obtained by photographing its shadow were inaccurate because of the inertia of the instrument Laboriously the electric heart tracings or electrocardiograms were obtained and corrected and considerable progress in their analysis was made by physiologists at the end of the last century (Bayliss and Starling 1892) and at the beginning of the present century Finally in 1903 came the announcement of the invention of the accurate and practicable string galvanometer (Einthoven) a few years later this was introduced into hospitals and clinical electrocardiography began

Einthoven W Die galvanometrische Registrirung des menschlichen Elektrokardiogramms zugleich eine Beurtheilung der Anwendung des Capillar Elektrometers in der Physiologie *Pfluger's Arch f d ges Physiol* 1903 XCIX 472

(Page 474) I have tried to find a way to avoid as far as possible the construction of a new curve [that is a corrected curve such as it was necessary to construct in the use of the capillary electrometer] in so doing I have at length devised an instrument which satisfies many requirements and is especially suitable to inscribe the human electrocardiogram directly in almost its exact proportions

The essential part of this instrument—the string galvanometer—is a thin silver coated quartz fibre which is stretched like a string in a strong magnetic field If

an electric current is led through this quartz fibre the fibre shows a movement which can be observed and photographed by means of considerable magnification, just as is the case with the movement of the mercury in the capillary electrometer It is possible to regulate the sensitivity of the galvanometer very accurately within wide bounds by tightening and loosening the string (Translation by myself)

During the past three decades with the development of audion tube amplification the dead beat mirror galvanometer has been adapted to clinical electrocardiography and is the basis for much of the easily portable apparatus that can be carried to the sickroom for cardiac registration of patients at home in bed The cathode ray has also been utilized to record the electrical activity and sounds of the heart in man but it is unnecessarily expensive in cost and in the use of high operating voltage for the needs of clinical electrocardiography and phonocardiography although in current research it is being utilized with extensive chest leads to explore details of the course of electrical discharge and repolarization through the heart muscle (Goldman) *

A recent innovation has been the utilization of an ingenious device of a heated stylus which activated by a galvanometer moves without friction or overshooting over the surface of a moving processed (wax covered) paper strip to inscribe the electrocardiogram directly without the trouble time and expense of photographic technic This type of direct writing electrocardiograph has the advantage of accuracy in recording over the initial ink writing galvanometers which were originally introduced to simplify the clinical technic

At first electrocardiography was sought and used chiefly as an aid in the explanation of cardiac arrhythmia tachycardia and bradycardia having proved to be more satisfactory than the mechanical graphic methods previously employed because of the greater ease of technic and interpretation and because of the more complete information afforded As time went on however it was learned that more important data about the heart than the explanation of abnormalities of rate and rhythm are shown by the electrocardiogram from a study of the shape direction amplitude and time relations of the individual waves or deflections especially as they are compared in various leads

It is unfortunate that we do not even as yet know the range of the normal electrocardiogram it is wider than we thought it was ten years ago and much service can still be wrought by the simple electrocardiographic analysis of many thousands of normal individuals It is also important to become familiar with the electrocardiogram in infancy which is different from that in older children and adults not only in much faster heart rate but in much narrower time intervals especially *P R* interval and *QRS* duration (shorter by one third to one half—see Figure 54 page 214) and in its normal right axis deviation It is interesting that the human infant s type of electrocardiogram becomes recognizable at the end of the first month of fetal life (Marcel and

* Recently cathode ray electrocardiography by radio (remote control) has been introduced by Holter of Helena Montana (1949) and by Kanatsoul s of Athens Greece (1950)

Exchaquet 1938) also exploration of the maternal abdomen to obtain fetal electrocardiograms has been found successful in 85 to 90 per cent of cases (Goodyear et al 1942)

The electrocardiograph does not take the place of such other methods of examination as history taking percussion auscultation and roentgenology but it does obviate in large part the need of taking mechanical graphic records of arterial and venous pulses and of the apex impulse *Finally it must be realized that the electrocardiogram may be perfectly normal even in the presence of serious heart disease* This method of study should therefore be viewed modestly as helpful but not accorded too great importance

The electrocardiogram itself is written by the spread of electrical activity that sweeps down the heart from its pacemaker at each heartbeat in peristaltic waves over the atria and by special conduction tracts and fibers into the ventricles (Figure 39)

It is the movement of the string shadow or beam of light that causes the waves (usually called deflections or complexes) of the electrocardiogram

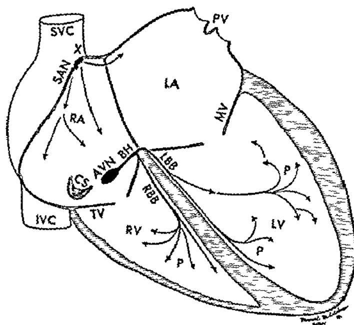


FIG 39 Diagram of excitatory and conduction system of the heart

SVC superior vena cava
IVC inferior vena cava
RA right atrium
CS coronary sinus
TV tricuspid valve
RV right ventricle
PV pulmonary veins
LA left atrium
MV mitral valve
LV left ventricle
SAN sinoatrial node
X usual site of pacemaker
AVN atrioventricular node
BH bundle of His
RBB right bundle branch
LBB left bundle branch
P Purkinje network radiating out from papillary muscles

(Graybiel and White s *Electrocardiography in Practice* W B Saunders C Philadelphia)

These waves chiefly three have been variously named The German school at first labeled them *a* for atrial wave *i* for the first or initial ventricular wave and *f* for the second or final ventricular wave these designations have been justified by time but they have not been generally adopted Einthoven s letters arbitrarily taken from the middle of the alphabet and attached to the deflections so as not to prejudice future workers in the study of the cardiac mechanism have become universally employed and will be used here the first deflection or atrial wave is called *P* the second deflection or the first ventricular wave a rapid succession of one two or three deflections is called *Q* *R* and *S* and the third deflection or second ventricular wave is called *T* (Figure 40) There is often a small final and unexplained wave called *U*

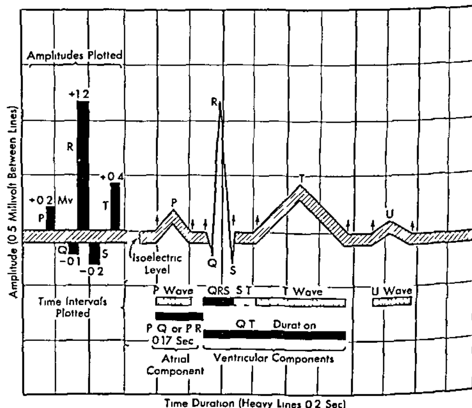


FIG 40 Diagram of normal electrocardiogram showing the individual complexes with special reference to amplitude and time duration *P* = atrial deflection *QRS* = first ventricular deflection *ST* segment and *T* wave = remainder of ventricular activity beginning of *Q* to end of *T* = duration of systole

There are two essential methods of description of the normal and abnormal electrocardiogram (1) that of the detailed analysis of the individual complexes or waves which will be largely covered in the present chapter and (2) that of the presentation of the characteristics of the records as a whole that is of the patterns which will be presented largely in other chapters for

example the electrocardiographic patterns of certain congenital defects of mitral stenosis of the hypertensive heart and the cor pulmonale of pericarditis and of myocardial infarction

ELECTROCARDIOGRAPHIC LEADS

The first and fundamental step in studying electrocardiograms is to become familiar with the so called electrocardiographic leads An electrocardio graphic lead is the connection of any two parts of the body by electrodes and wires with the recording galvanometer Although two electrodes may be at tached to any parts of the body (if they are not both too far from the heart or too close together) to lead the heart current to the galvanometer it has become customary for convenience and other reasons to make use clinically of the forearms the left leg and the precordium An esophageal lead point to explore the left atrium and base and posterior portion of the left ventricle has been proposed and tried with results of some interest but the procedure is not clinically practicable

Direct leads from various points on the heart surface itself present the most detailed information possible concerning the spread of the excitation wave and aberrations thereof to the individual heart chambers and their anterior posterior and lateral walls The best substitute for such direct leads in man has been found to be precordial leads with exploring electrode placed on the skin as directly as possible over the part of the heart which it is desired to study Thus many thoracic lead points are possible in the various intercostal spaces and around the chest and even in the esophagus We have not yet nearly enough information to be sure of the most desirable positions and indeed they are already known to vary from person to person according to the body build and the position and type of heart disease but certain points have already been selected and made the object of considerable study in normal and abnormal subjects more about these below An important con sideration in obtaining these precordial or close up leads is that the other or as it is sometimes called indifferent remote or peripheral electrode should be placed far from the heart itself on one of the extremities or on the back or by an ingenious arrangement introduced by Wilson to neutralize the effect of any one extremity by connecting all four extremities to a central terminal as the remote electrode point The concentration of interest on the precordial leads initiated what has been called essentially a unipolar lead

Quickly following suit unipolar limb leads have been introduced to join the unipolar and bipolar chest leads they were at first in major part elaborated by Goldberger (1947) In the early days of these so-called unipolar limb leads it was thought that they had a rather mysterious superiority over the old classical bipolar limb leads particularly in revealing more accurately the electrical (and also often the anatomic) position of the heart and otherwise obscure myocardial disease but more recently it has been shown by Gr and others that they actually merely supplement the bipolar limb

allows us to establish with greater accuracy the projection of the axis and abnormalities thereof on the frontal plane of the thorax thus expanding Einthoven s triangle (see below) into a figure with six axes the three of the unipolar leads being perpendicular to the three of the bipolar leads so that there is only a 60 degree instead of a 120 degree interval between the axes (as will be illustrated later in the chapter)

Although the very first published electrocardiogram (Waller 1887) was a chest lead convenience and chance led early electrocardiographers away from the thorax itself to limb connections and only in late years has there been a return to the precordium as an important focus of attention The pre cordial leads at this writing (1950) appear to have a double value as com pared with the limb leads they reveal the electrical axis projection on the anteroposterior (more or less sagittal) plane at right angles to the frontal plane thus completing the resultant projection of the direction and magnitude of the electrical axis in space but also because of their close proximity to the heart itself they show more clearly myocardial abnormalities closest to them Nevertheless it is not likely that the limb leads as now taken will be abandoned soon inasmuch as they readily reveal normal variations and abnormalities in the frontal plane The heart is a solid body and so should be explored electrically from all directions Eventually technics such as those developed by Duchosal and by Goldman (see below) or something newer still may replace the present procedures but as yet they have not been developed for practical routine use

In summary the reasons for taking these three types of leads are as fol lows We continue to register the *bipolar limb leads* because we are familiar with them after many years of use, because they clearly suffice to demonstrate the mechanisms responsible for tachycardia bradycardia and arrhythmia because they are important in helping to establish the projection of the electrical axis and abnormalities thereof in the frontal plane and because they have become in many instances a part of the useful electrocardio-graphic patterns with which we have become familiar during the past decade such as those of the acute cor pulmonale congenital atrial septal defect and advanced mitral stenosis (or chronic constrictive pericarditis involving preponderantly the left heart chambers) The *unipolar limb leads* are registered because they are especially helpful in demonstrating the position of the heart with or without complications of heart disease itself thus the right arm lead always (except in cases with dextrocardia) faces the interior of the heart and so normally all its complexes are inverted the left arm faces the outside wall of the heart when the heart lies horizontally or diagonally with resultant upright complexes and the inside of the heart (as does the *right arm lead) when the heart is vertical giving inverted QRS and T* waves the left leg lead never faces the inside of the heart although it is at right angles to its axis when it lies horizontally thus yielding under such conditions small almost isoelectric complexes The *unipolar precordial leads* are registered because of their double value just discussed in the preceding paragraph

Thus ordinarily now the three bipolar and the three unipolar limb leads

and several (preferably six) precordial leads are registered for each patient studied these leads have been called Leads 1 2 3 aVR aVL aVF and Precordial or Chest Leads 1 to 6 or more respectively (Figure 41) In routine interpretation at the present time (1951) it is convenient to analyze first the precordial leads since they often give the most information

BIPOLAR (CLASSICAL) LIMB LEADS

Lead 1 consists of the connection of the right lower arm to one end of the galvanometer string and of the left lower arm to the other end so that the preponderant spread of the action current (which has been called the wave

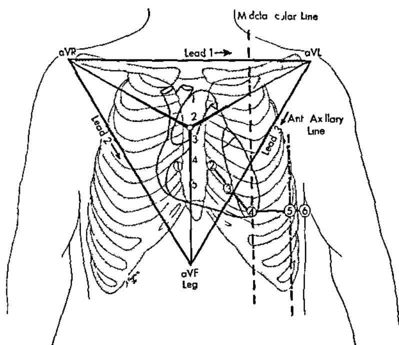


FIG 41 Diagram showing bipolar limb leads (1 2 3) unipolar limb leads (aVR aVL, aVF) and precordial leads (V to V inclusive) The outline of the heart is shown under the sternum and ribs the level of the first five interspaces is indicated Einthoven s triangle is represented as is also the spatial relationship of the remote electrode to the limb electrodes in the case of the unipolar limb leads

of relative negativity) in the direction of the lead that is from right arm to left is represented normally in the electrocardiogram by an upright deflection of the string shadow while its reverse direction is represented by an inverted deflection

Lead 2 consists of a similar arrangement but with electrodes on right arm and left leg Either leg may be used with little or no change in the records obtained since both legs show almost the same difference of electric potential

allow us to establish with greater accuracy the projection of the axis and abnormalities thereof on the frontal plane of the thorax thus expanding Einthoven s triangle (see below) into a figure with six axes the three of the unipolar leads being perpendicular to the three of the bipolar leads so that there is only a 60 degree instead of a 120 degree interval between the axes (as will be illustrated later in the chapter)

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possible over the cardiac apex However it rather quickly became apparent that even with care it was not always possible so to place it that even though it were so placed it would usually emphasize normality or abnormalities of but a localized area of the heart wall and that it might be so close to the ventricular sulcus or so perpendicular to the spatial axis of the heart that a slight displacement to either side would shift its position from one ventricle to the other or from negative to positive side of the anteroposterior plane of the thorax (or vice versa) with a great change in the pattern Therefore an isolated *Lead 4* was given up by most workers in the field a few years ago

It was also stated in the last edition of this book that multiple precordial (chest) leads should be taken in special or doubtful cases and that the author and his colleagues were taking three such leads (CF CF_4 and CF_5) when necessary rarely more at that time Our own experience and that of many others soon caused us to take three precordial leads routinely with the exploring electrode at points 2 4 and 5 and as time went on over 2 4 and 6 instead and with Wilson s central terminal (V) for the indifferent lead point instead of the left leg (as had been our choice) or the right arm (as was often the choice of others) Finally with more experience in the course of time we began to take all six precordial V leads in addition to the six limb leads mentioned above so that for the sake of the valuable extra information afforded we now take 12 routine leads instead of the 3 that we took at the time of the first edition of this book (1931) the 4 that we frequently took at the time of the second edition of the book (1937) and the 6 that was our custom at the time of the third edition of the book (1944) In fact on occasion we may now explore further still as in the case of a special atrial lead (high up over the right atrium) or of a lead (sometimes called 7) on the back at the left posterior axillary line It is still too early to know how far we had best explore and just what technics we shall eventually use

Multiple precordial leads (Figure 41) have become standardized as follows the prefix depending on the position of the indifferent electrode or lead point—CR (chest—right arm) CL (chest—left arm) CF (chest—left leg) and CV usually abbreviated now to V

1 or CR_1 CL_1 CF_1 CV_1 or V_1—the exploring electrode at the *right* border of the sternum in the fourth intercostal space

2 or CR CL CF CV or V—the exploring electrode at the *left* border of the sternum in the fourth intercostal space

3 or CR_3 CL_3 CF_3 CV_3 or V_3—the exploring electrode midway on the line joining 2 and 4

4 or CR_4 CL_4 CF_4 CV_4 or V_4—the exploring electrode at the left midclavicular line in the fifth intercostal space We used to try to place this electrode at the cardiac apex but the variability of the position of the latter both in health and in disease rendered that location very unreliable and unsatisfactory

5 or CR CL CF CV or V—the exploring electrode at the anterior

during the cardiac cycle the left leg is however the customary lower point

Lead 3 consists of the connection of the galvanometer with left arm left leg in comparison with Lead 2 the left leg lead continues to be the [illegible] contact while the left arm is substituted for the right arm

Thus these three lead points right arm left arm and left leg when c[illegible] nected form a triangle which is essentially equilateral Electrically and [illegible] metrically Lead 2 is equal to the sum of Leads 1 and 3 since the differe[illegible] of electric potential between right arm and left leg is the same whether [illegible] connect the lead points directly or in a roundabout way Therefore the [illegible] P_2 should equal P_1 plus P *QRS* should equal QRS_1 plus QRS_3 and *T* sho[illegible] equal T_1 plus T_3 (these letters refer to atrial and ventricular deflections in th[illegible] electrocardiogram soon to be discussed while the appended numbers refer t[illegible] the particular leads—1 2 and 3) Similarly Lead 2 minus Lead 1 equals Lead 3 and Lead 2 minus Lead 3 equals Lead 1 This fact although useful clinically in checking the accuracy of standardization of the various leads is often ignored

UNIPOLAR LIMB LEADS

Lead aVR is the new customary so called augmented (a) that is amplified 50 per cent unipolar (V a symbol) right arm (R) lead The exploring el[illegible] trode is attached to the right arm and connected to one pole of the galvanometer while the other pole is connected to the indifferent lead point which in the case of the unipolar limb leads has been found to serve best when attached to the three limbs not being explored V is a designation introduced by Johnston—personal communication 1951—to indicate leads taken with a central terminal and derived from its usage by electrical engineers and physicists as a symbol of electrical potential it was not originally intended as an abbreviation for vector

Lead aVL is the augmented unipolar left arm lead with exploring electrode on the left arm and indifferent lead point connected to the right arm and both legs

Lead aVF is the augmented unipolar left leg (F for foot) lead with ex ploring electrode on the left leg and indifferent lead point connected to both arms and right leg

It is important and convenient to know that when added together the three unipolar limb leads aVR aVL and aVF equal zero

PRECORDIAL (CHEST OR THORACIC) LEADS

In the last (third) edition of this book much was said about *Lead 4* which had been called the standard or indeed even the classical" chest lead It had been taken by attempting to place the exploring electrode as near as

ighth and ninth leads over the left back and right anterior chest leads numbered from midline to the right like the precordial leads and as advised by Kisch with the first lead point at the midsternum (level of fourth interspace) for both sides

It is obvious that the unipolar chest leads taken as Wilson has recommended (CV) leads give a more accurate appraisal of the potential at the various precordial lead points than do the bipolar leads although there is by no means so great a difference as in the case of the unipolar and bipolar

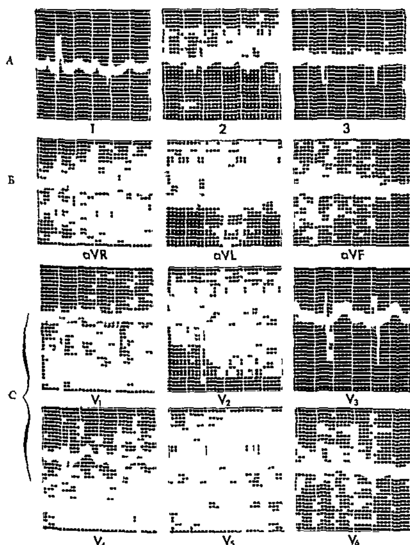


FIG 43 Electrocardiogram of normal individual of heavy build with horizontal heart position (*A*) Bipolar limb leads 1 2 and 3 (*B*) unipolar limb leads aVR, aVL, and aVF (*C*) six precordial leads V to V inclusive Time = 0 04 and 0 20 second amplitude 1 mm = 0 10 mv

limb leads This is of course due to the fact that the greater the difference in distance of two electrodes from the heart the less the error due to the potential of the point to which the indifferent electrode is attached Thus the bipolar chest leads described above approach in accuracy the unipolar chest leads of Wilson For this reason and especially for the sake of universal uniformity it is suggested that for routine use the V leads be now employed as has been my own recent custom

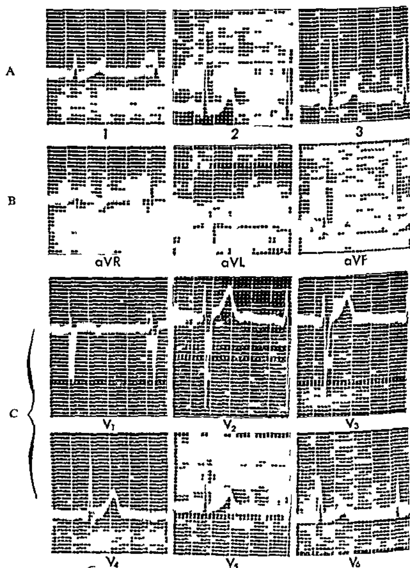


FIG 44 Electr... logram of normal tall individual with vertical heart position. (*A*) Bipolar limb ... 1 2 and 3 (*B*) unipolar limb leads aVR aVL, and aVF (*C*) six precordi... V to V inclusive Time = 0 04 and 0 20 second amplitude mm = 0 10 mv

Intracardiac and esophageal leads have been used in research and for study of very special cases the former during catheterization of the right atrium and right ventricle and the latter for exploration of the left atrium and posterior wall of the left ventricle They serve as unipolar leads to explore these particular parts of the heart and although during acute myocardial infarction it is not wise to subject the patient to esophageal electrocardiography it is possible in chronic cases to identify a posterior myocardial scar and also to uncover atrial action not apparent in other leads The right intra atrial electrocardiogram shows normally an inverted *P* wave high in the atrium in the vicinity of the s a node an upright *P* wave low in the atrium and a diphasic *P* wave in intermediate positions while the ventricular complex varies from a *QS* to a *QR* most commonly or even less often (near the ventricle) to a *RS* all with negative *T* waves The right intraventricular electrocardiogram shows normally an upright *P* wave and an *RS* with a negative *T* Esophageal leads show a slightly later *P* wave over the left atrium by about 0 05 second than the *P* wave recorded by the right intra atrial electrode

In the esophageal lead the *P* wave is as a rule unusually prominent and high and the *QRS* and *T* waves are normally inverted unless the polarity is reversed in which case an inverted *T* wave is indicative of disease (usually infarction) of the posterior wall of the left ventricle

CARDIAC VECTOR AND ELECTRIC AXIS

A vector is a force which has direction and magnitude and electrically either a negative or a positive charge In electrocardiography it has been loosely called the electrical axis of the heart Fundamentally electrocardiography is the analysis of the cardiac electrical vectors and there are various technics for their demonstration all of which are more or less crude and in the process of further development including the old classical bipolar limb leads with the much debated but still scientifically applicable Einthoven triangle the unipolar limb leads the precordial leads and the more basic but least developed technic of all namely that of vectorcardiography

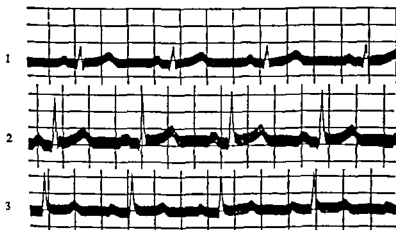
When the excitation wave spreads from normal or abnormal pacemaker through the heart it is attended by a wave of electric activity which takes a complicated manifold path (see Figure 39 page 183) The diffuse course can be represented by the *QRS* loop a curve not lying in a single plane but in space as does the heart itself A further reduction of this curve has hitherto been necessary to suit the limited boundaries of electrocardiography and so we can determine its projection on the anterior plane of the body to fit into the triangle of the three classical leads or on any other plane for example specifically sagittal or horizontal Finally for further convenience the curve is simplified by constructing its resultant a straight line to show the consequent angle and magnitude This resultant of the projection of the true axis of the distributed electric potential of the heartbeat is what we briefly designate as the electric axis of the electrocardiogram It can be determined by calculation

from any two of the three classical limb leads by formula or by diagram usin what is called Einthoven s triangle It has been of some clinical interest an value to make this calculation in cases showing an abnormal deviation of th angle (the normal range of angle is from −20 to +100 but usually +?0 to +70°) The formula is as follows *tangent of alpha* $= \frac{2e - e_1}{e_1\sqrt{3}}$ whe alpha equals the angle between the axis and the horizontal *e* the amplitud in millimeters of the *QRS* wave in Lead 2 and e_1 that of the *QRS* in Lead 1 The length of the axis or the manifest potential difference (E) is calculate from the following formula $E = \frac{e}{\cos(\alpha - 60)}$ More convenient than the formulas has been the employment of the diagram of the triangle of th leads (Figure 45 Einthoven s triangle) Leads 1 and 3 are usually employe in this calculation The amplitude of $R_1 - S_1$ is plotted on the Lead 1 lin and that of $R_3 - S_3$ on the Lead 3 line perpendiculars are dropped from the points to their points of intersection Lines are then drawn out from the cente of the circle through these points of intersection to the circumference of th circle the angles with the horizontal diameter of the circle the zero line ar read off the degrees being noted as positive around the semicircle clockwis to 180 and as negative counterclockwise This is a crude but clinically cor venient and useful method It affords only a very general measurement an- shows no detail of the axis deviation If at the present time however greater detail and accuracy are attempted the method becomes complicated and diffi cult Although it is of some academic interest to know not only the resultant axis deviation but its whole curve that is the individual deviations at various phases it is of much greater interest to know the direction of the curve in space for example how much of it is bent backward in the anteroposterior plane a feature not shown at all in the frontal plane It is to be noted that to secure adequate information accurately for even one (e g the frontal) plane two electrocardiographic leads must be registered simultaneously to make sure of the synchronicity of phases for example the top of the *QRS* peak in Lead 1 is often not synchronous with either peak (or nadir) of downstroke in Lead 3 A further development of the representation and analysis of the cardiac vector (electric axis) in space has been the construction of the vectorcardiogram both by projection on the three planes and by tridimensional models (see below)

The direction of the resultant electric axis of the heart in the frontal plane lies within wider limits than does the anatomic axis both normally and ab- normally The normal electric axis lies between the degrees −20 and +100 of Einthoven s triangle (Figure 45) If the angle is more minus than −20 that is much above the horizontal there is so-called abnormal *left axis* devia tion and if it is beyond +100° that is considerably to the right of the vertical there is abnormal right axis deviation

The term abnormal left and right axis deviation as applied to the classical bipolar limb leads does not have the same significance as left and ri ht

ventricular preponderance Displacement of the heart upward by a high diaphragm so that the heart lies horizontally will give abnormal left axis deviation even though the left ventricle remains normal while a low diaphragm with vertical heart position will tend to give abnormal right axis deviation even though the right ventricle is small and the left ventricle actually preponderant It is true however that when we find high degrees of abnormal



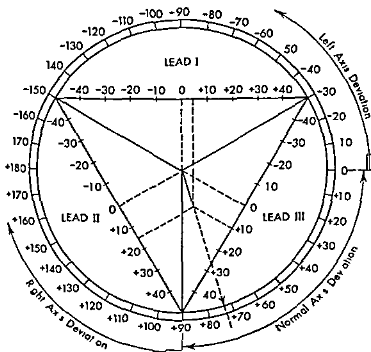
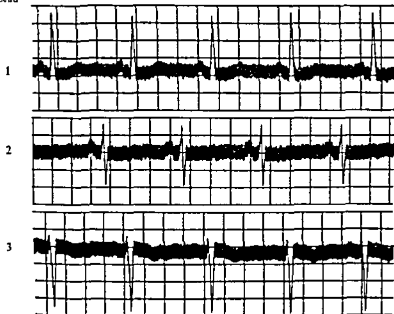


FIG. 45 Electrocardiogram (Leads 1 2 and 3) and Einthoven s triangle showing normal angle of the electrical axis

from any two of the three classical limb leads by formula or by diagram using what is called Einthoven's triangle. It has been of some clinical interest and value to make this calculation in cases showing an abnormal deviation of the angle (the normal range of angle is from $-20°$ to $+100$, but usually $+30$ to $+70°$). The formula is as follows: tangent of alpha $= \frac{2e - e_1}{e_1\sqrt{3}}$, where alpha equals the angle between the axis and the horizontal, e the amplitude in millimeters of the QRS wave in Lead 2, and e_1 that of the QRS in Lead 1. The length of the axis, or the manifest potential difference (E), is calculated from the following formula: $E = \frac{e}{\cos(\alpha - 60)}$. More convenient than these formulas has been the employment of the diagram of the triangle of the leads (Figure 45, Einthoven's triangle). Leads 1 and 3 are usually employed in this calculation. The amplitude of $R_1 - S_1$ is plotted on the Lead 1 line and that of $R_3 - S_3$ on the Lead 3 line; perpendiculars are dropped from these points to their points of intersection. Lines are then drawn out from the center of the circle through these points of intersection to the circumference of the circle; the angles with the horizontal diameter of the circle, the zero line, are read off, the degrees being noted as positive around the semicircle clockwise to 180, and as negative counterclockwise. This is a crude but clinically convenient and useful method. It affords only a very general measurement and shows no detail of the axis deviation. If at the present time, however, greater detail and accuracy are attempted the method becomes complicated and difficult. Although it is of some academic interest to know not only the resultant axis deviation but its whole curve, that is, the individual deviations at various phases, it is of much greater interest to know the direction of the curve in space, for example, how much of it is bent backward in the anteroposterior plane, a feature not shown at all in the frontal plane. It is to be noted that to secure adequate information accurately for even one (e.g., the frontal) plane two electrocardiographic leads must be registered simultaneously to make sure of the synchronicity of phases; for example, the top of the QRS peak in Lead 1 is often not synchronous with either peak (or nadir) of downstroke in Lead 3. A further development of the representation and analysis of the cardiac vector (electric axis) in space has been the construction of the vectorcardiogram, both by projection on the three planes and by tridimensional models (see below).

The direction of the resultant electric axis of the heart in the frontal plane lies within wider limits than does the anatomic axis, both normally and abnormally. The normal electric axis lies between the degrees -20 and $+100$ of Einthoven's triangle (Figure 45). If the angle is more minus than $-20°$, that is, much above the horizontal, there is so-called abnormal left axis deviation, and if it is beyond $+100°$, that is, considerably to the right of the vertical, there is abnormal right axis deviation.

The term "abnormal left and right axis deviation" as applied to the classical bipolar limb leads does not have the same significance as "left and right



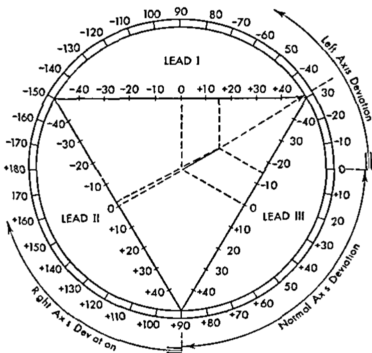


FIG 46 Electrocardiogram and Eintho en s triangle showing left axis deviation

average normal angle to an abnormal one (Figure 4 page 33) This influence of displacement may even give abnormal left axis deviation of great degree although it often but exaggerates the effect of other factors An interesting variation of this type consists of complete negativity of Lead 3 all the complexes—*P* *QRS* and *T*—being inverted this phenomenon is often found in short fat individuals with high diaphragms

2 Preponderant enlargement of the left ventricle is a common cause or accompaniment of left axis deviation of high degree Chronic hypertension and chronic aortic regurgitation or stenosis are the most important of the known clinical conditions behind it (see Figure 97 page 477 and Chapter 26)

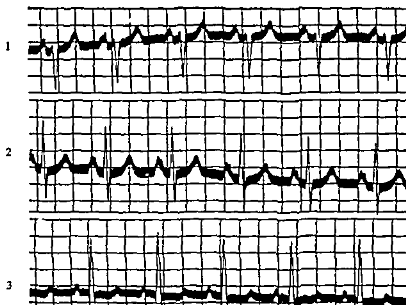
3 Left bundle branch block (see Chapter 34) The electrocardiogram of marked left bundle branch block has abnormally wide *QRS* waves over 0 1 second in duration with moderate amplitude above the baseline in Lead 1 and below the baseline in Lead 3, with rather low voltage or diphasic *QRS* waves in Lead 2 (see Figure 165 page 947) and broad notched downwardly directed *QRS* waves over the right ventricle and bifid or slurred *R* waves over the left in the multiple precordial leads Until fifteen years ago this type of electrocardiogram was thought to indicate right bundle branch block but convincing evidence from the precordial leads (with late arrival of the intrinsic deflection over the left ventricle) exposed the error of the earlier interpretation

4 Right ventricular premature beats (see Chapter 32) Isolated instances of abnormal axis deviation occur in the form of ventricular premature beats arising in the right ventricle or near the cardiac base The *QRS* waves are deformed much as in left bundle branch block but their amplitude is usually much greater In a well marked instance of right ventricular premature beat the QRS_1 is relatively high the QRS_3 is deep the *QRS* is diphasic and often of low voltage and the precordial *QRS* shows an early intrinsic deflection over the right ventricle Years ago these extrasystoles were thought to arise in the left ventricle

Abnormal right axis deviation (Figure 47) much less common than abnormal left axis deviation results from five factors

1 A vertical heart position or rotation of the heart on its other axes may give rise to abnormal right axis deviation usually not of great degree the angle rarely measuring more than +95° in the normal person but sufficient to mask other conditions It is by far the commonest cause of right axis deviation Deep inspiration may give temporarily a slightly abnormal right axis deviation when the electrocardiogram in quiet breathing shows a tendency toward it Displacement of the heart to one side or the other by fluid or by air in the pleura or by lung retraction or pleural adhesions affects the position of the heart as a rule in toto along with the mediastinum without causing any important change in axis deviation as does also shifting of position from one lateral recumbency to the other as noted above

2 Preponderant enlargement of the right ventricle with its attendant shift in position of the heart particularly by clockwise rotation is the commonest



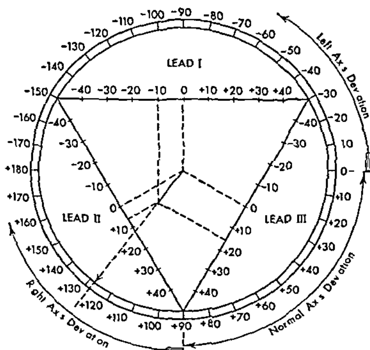


FIG 47 Electrocardiogram and Einthoven's triangle showing abnormal right axis deviation in a case of mitral stenosis of high degree

cause of markedly abnormal right axis deviation in which there is a sharp moderately deep S_1 with little or no R_1 a diphasic *QRS* of little voltage a high R_3 with little or no S_3 and relatively high R waves over the right ventricle and prominent *S* waves over the left ventricle in the precordial leads During the first few weeks of life right axis deviation is often present normally in slight degree After that age moderate or high degrees of right axis deviation are caused by three clinical conditions mitral stenosis congenital defects and pulmonary disease Mitral stenosis is frequently found without abnormal right axis deviation but when that electrocardiographic sign is present especially if there is atrial fibrillation and no obvious sign of congenital heart disease that valve lesion is usually found to be present (Figure 129 page 680) Congenital pulmonic stenosis and interatrial septal defects are rarely if ever found without abnormal right axis deviation by electrocardiogram they cause a higher degree of it than does any other condition (see Figure 73 page 320) Rarely the cause of abnormal right axis deviation is chronic pulmonary disease in particular silicosis or other cause of extensive fibrosis Very rarely pulmonary endarteritis may be a factor

3 Right bundle branch block is shown electrocardiographically by abnormally wide *QRS* complexes directed downward in Lead 1 and upward in Lead 3 or by wide S_1 waves (see Figure 166 page 948) In Lead 2 the *QRS* wave is diphasic as a rule and of low voltage and in the multiple precordial leads it is M shaped over the right side of the heart and shows a prominent *R* wave and wide *S* wave over the left This was formerly called left bundle branch block (see Chapter 34)

4 Left ventricular premature beats are isolated instances of abnormal right axis deviation giving high wide *QPS* complexes in Leads 2 and 3 *QRS* waves often of low voltage slightly or moderately inverted in Lead 1 and with wide *QRS* waves in the precordial leads with earlier intrinsic deflections over the left ventricle A premature beat arising from the left ventricle although near the right ventricle has been shown experimentally to give rise to a *QRS* complex of left ventricular premature beat type But ventricular premature beats are often neither of definitely right nor of definitely left ventricular type in the electrocardiogram in such cases they may arise in the septum or junctional tissue

5 Congenital dextrocardia shows a typical electrocardiogram in about half the cases that is where there is transposition with general situs inversus (see Figure 65 page 303) There is a complete inversion of all complexes of Lead 1 and an interchange of the usual Leads 2 and 3 due to the fact that with relation to the heart in such a case the right arm corresponds to the left arm of the person with the heart in normal position and the left arm to the right When an electrocardiogram shows a completely inverted Lead 1 it is pathognomonic of congenital dextrocardia provided there is no error in technic namely a crossing of electrode wires The precordial leads show the usual normal characteristics when the exploring electrode is placed over the right side of the chest

Vectorcardiography A further and natural evolution of the study of the cardiac vector is its determination and demonstration in space that is in three dimensions and also in time which is of prime importance too since the duration as well as the distance direction and magnitude of the cardiac vector is significant Various technics have been introduced to study the vector projected on the frontal plane as already noted including among others that recently devised by Goldman using the cathode ray oscillograph and many lead points over the entire precordium which result in waves of darkness and light representing *P* *QRS* and *T* waves sweeping over the field

Also desirable as an eventual goal when it can be routinely introduced is the spatial (and time) recording of the cardiac vector which has been called vectorcardiography Various investigators have studied the problem Mann was one of the first who did so calling the resulting curve the monocardiogram (1920 and 1938) Duchosal and Sulzer (1949) are also pioneer workers who have developed the method more fully with the actual construction of models of the *P* *QRS* and *T* waves (vectorcardiography) based on the projections of cathode ray oscillograms of the cardiac vector on two planes of a trihedron with the time marked off by beads attached to the wire loops representing the course of the vectors (Figure 48) Figure 49 shows the relationship of the trihedron of Duchosal and Sulzer to Einthoven s triangle and the unipolar chest lead points Much time will be needed to determine the range of normal vectorcardiograms and abnormal patterns

My friend and former associate Dr J W Hurst of Atlanta Georgia experienced in recent developments in certain technics of the application of vectorcardiography in this country has kindly prepared for me the following insert (personal communication March 1951)

Grant and his co workers have presented a method for determining the spatial direction of the fundamental electrical forces of the heart by simple inspection of routine electrocardiographic leads Since this method appears promising it is mentioned here for completeness For greater details and proof of the method the reader is referred to the Bibliography

To d termine the direction of the mean *QRS* *ST* and *T* forces in the frontal plane the six extremity leads are inspected to determine which lead has the largest deflection and which lead has the smallest deflection The resultant area of each deflection is used to determine its relative size The resultant area is determined by adding the positive portions of the curve to the negative portions algebraically The mean vector will be parallel to the lead axis with the largest resultant deflection or perpendicular to the lead axis with the smallest resultant deflection and its direction must satisfy the polarity of all six extremity leads With practice one will soon learn to interpolate between the extremes of vector positions just mentioned so that the range of error will be only 5 to 10 degrees The direction of the instantaneous vectors can be determined in a similar manner by breaking up the *QRS* and *T* deflections into small individual portions If one remembers that Lead 1 + 3 = 2 and that aVR + aVL + aVF = 0 then the determination of the direction of

the various vectors becomes quite accurate By the above reasoning one can determine the frontal plane projection of the mean spatial *QRS ST* and *T* vectors and spatial *QRS ST* and *T* loops

After identifying the direction of the frontal plane projection of a spatial vector one then locates the transitional complex in the precordial leads (A transitional complex is equally negative and positive or resultantly zero) The transitional complex is recorded along the transitional pathway on the chest which is produced by a plane perpendicular to a spatial vector at its origin extended to the surface of the volume conductor The location of this plane which is perpendicular to the spatial vector under study will therefore deter

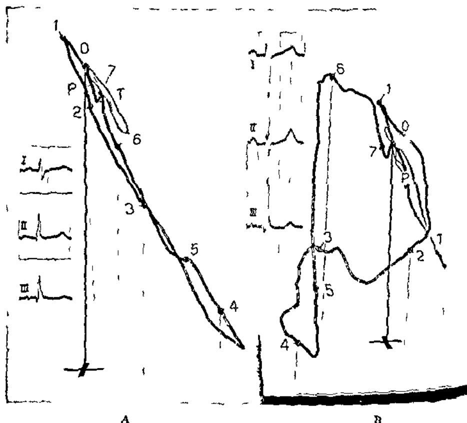


FIG 48 (*A*) Photograph of wire loop representing the vectorcardiogram of a normal individual *The timing of the long obliquely placed QRS loop indicated by heavy black wire* is shown by beads from 0 to 7 (time interval = 0 01 second) The *P* loop is made of thin wire scarcely visible The *T* loop is grey in color The point of origin of all three loops *P QRS* and *T* is zero A black column supports the model At the *bottom of the stand a cross represents the normal axes of the body the vertical bar the antero-*posterior and the horizontal bar the transverse The electrocardiogram (limb leads I II and III) is shown at the left of the loop (*B*) Wire loop representing the vectorcardiogram of a case of the tetralogy of Fallot with the graphs of the complexes and the *electrocardiogram represented* as in the case of *A* (Kindness of Dr Pierre Duchosal Geneva Switzerland)

mine the anterior or posterior displacement of a vector from the frontal plane thus identifying its spatial position If the thorax is assumed to be a cylinder which is a reasonable assumption electrically speaking it is quite easy to visualize the transitional pathway and its relationship to the spatial vector The method described allows one to determine the mean spatial vectors and by similar reasoning the spatial instantaneous vectors can be visualized The range of error in determining the spatial direction of electrical forces approaches 15 degrees

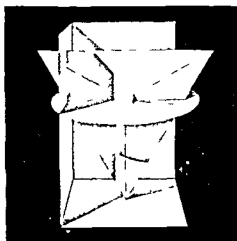


FIG 49 Drawing in perspective of the plans of derivations according to several systems The rectangular trihedron symbolizes the derivations of the vector the equilateral triangle that of the limbs and the ellipse those of the precordium (Kindness of Duchosal and Sulzer Figure 43 page 88 of their book *La Vectocardiographie* S Karger Bale and New York 1949)

In a general sort of way the *QRS* vector indicates the direction of the electrical field in the chest and it becomes totally unnecessary to memorize various deflection contours in order to determine such a position The spatial *QRS T* angle is an extremely useful tool It should be apparent that the *QRS* vector and *T* vector produce the sides of the parallelogram which is necessary to construct the ventricular gradient and therefore the *QRS T* angle incorporates certain of the properties of the gradient The spatial *QRS T* angle varies with age and in the normal adult is usually less than 60 degrees

The electrocardiogram of a patient with a normal heart is shown analyzed by the vectoral method in Figure 50

The electrocardiogram of a patient with an extensive anterior myocardial infarction is shown analyzed by the vectoral method in Figure 51

Electrocardiographic gradient Closely related to the cardiac vector and the electric axis is the so-called gradient which may be calculated for either atria or ventricles although to date attention has naturally been focused as in other such studies on the ventricles The ventricular gradient as defined by Burch

and Winsor (1949) is a vector expression (in quantitative terms) of the relative variations in duration of the excited state in the different portions of the ventricular musculature Thus g (the ventricular gradient as projected on the frontal plane of the body) = the sum of A_{QRS} (the mean manifest magnitude of the *QRS* complex determined algebraically and measured in microvolt seconds or units i e the mean force of the depolarization process of the ventricular musculature) plus A_T (the mean manifest magnitude of the *T* wave which represents the repolarization process in microvolt seconds or units) The caret placed over the symbols indicates a vector value

The technic of the measurement of the ventricular gradient consists of

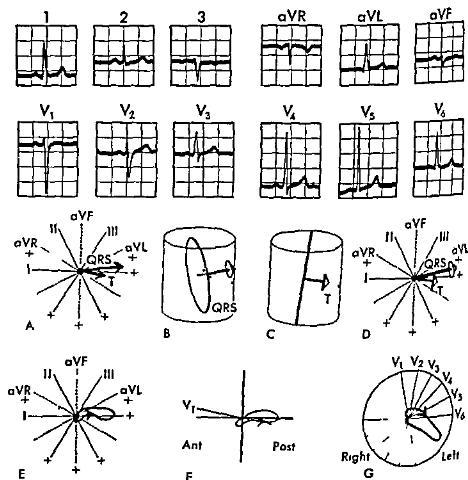


FIG 50 Thirty seven year-old normal male illustrating a horizontal position of the mean *QRS* vector (*A*) Mean *QRS* and *T* vectors as seen in the frontal plane (*B*) mean spatial *QRS* vector as seen in a cylindrical volume conductor (*C*) mean spatial *T* vector as seen in a cylindrical volume conductor (*D*) final "summary" figure to illustrate the spatial *QRS* and *T* electrical forces (*E*) frontal plane *QRS* loop (*F*) saggital plane *QRS* loop and (*G*) coronal plane *QRS* loop seen from below (Kindness of Dr J Willis Hurst Atlanta)

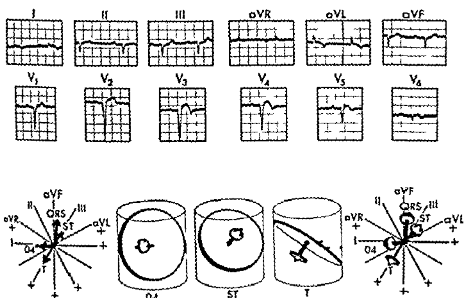


FIG 51 The electrocardiogram shown above is from a 50 year-old male with a characteristic history of myocardial infarction The figure to the left shows a six axial lead arrangement which is produced by superimposing the unipolar extremity lead axes on the tri axial reference system of Bayley This figure shows the frontal plane projection of the spatial *QRS* *ST* *T* and 04 vectors Note that the mean *QRS* is only slightly positive in Lead 1 and is negative in Leads 2 and 3 and also fits the polarity of the unipolar extremity leads The mean *T* vector is perpendicular to Lead aVR and therefore is largest in Lead 3 The mean *ST* vector is slightly negative in Lead aVR and the first 04 second of the *QRS* loop is approximately perpendicular to Lead aVF The edge of the circular disc represents the transitional pathway along which transitional complexes will be recorded The 04 second vector is tilted markedly posteriorly since the initial deflection is negative in Leads V The *ST* vector is tilted markedly anteriorly since the *ST* segment is elevated in all the chest leads The *T* vector is tilted only slightly anteriorly since the *T* wave is positive in Lead V and negative in Leads $V_{4,5,6}$ In general the 04 "dead zone vector is directed away from an area of myocardial infarction and the *T* vector is directed away from the ischemic zone surrounding the area of infarction The *ST* vector is directed toward the area of myocardial injury surrounding the area of infarction The tracing above represents an extensive anterior myocardial infarction since the 04 vector is directed away from the anterior ventricular wall and the *ST* vector points toward the same area The *T* vector is directed away from the lateral wall of the left ventricle The diagram to the right illustrates how the spatial vectors are recorded routinely in clinical practice (Figure and legend through the kindness of Dr J Willis Hurst Atlanta)

The 04 vector refers to the initial electrical force acting during the first 04 second of the *QRS* loop

measuring the sum of the areas (A) in microvolt (one millionth volt) seconds under the *QRS* and *T* waves above the baseline in any two leads (preferably Leads 1 and 3) and subtracting the sum of areas below the baseline (Figure 52A) In the case of a single normal muscle strip (Figure 52B) the gradient would be zero since the depolarization area (R) above the baseline would be neutralized by the repolarization area (T) below the baseline In human electrocardiography however the situation is very different there being many

heart muscle masses with varying individual influences per se and as affected by changes in position and rate of the heart as well as by disease Thus since in the frontal plane the routine limb leads show normally preponderant upright T waves as well as preponderantly upright QRS waves the normal *ventricular gradient in man has been found to average* +52 microvolt seconds or 13 0 units (1 unit = 4 microvolt seconds) the range is not certain but has been put at a maximum of 23 0 units and a minimum of about 2 5 units (Burch and Winsor 1949) The gradient of QRS (A_{QRS}) varies from about +12 0 to about −3 5 units There is as yet little clinical applicability of the ventricular gradient although primary changes in A_T (i e not dependent on variations of the QRS wave) may be distinguished by this method

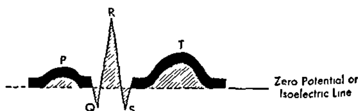


FIG 52A Diagram showing the areas subtended by the P and QRS complexes and the area under the T wave Areas above the isoelectric line are considered to be positive values and those below the isoelectric line are negative

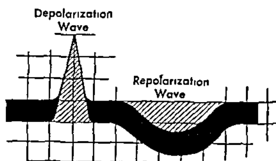


FIG 52B The process of depolarization and repolarization results in two separate waves which include areas of equal size (*A Primer of Electrocardiography* 2nd ed 1949 [1st ed 1945] Kindness of Drs George Burch and Travis Winsor and Lea & Febiger Philadelphia)

ELECTROCARDIOGRAPHIC COMPLEXES AND TIME INTERVALS

THE ATRIAL DEFLECTION OR *P* WAVE

The normal *P* wave Electrical activity of the atria is as a rule better defined and studied in Lead 2 than in the other routine leads because the axis of the P (atrial) wave is commonly parallel to Lead 2 for special analysis in difficult cases however the first precordial lead V_1 may be useful or, best of all a lead with electrode in the third interspace just to the right

of the sternum Analysis of the normally inverted P wave in Lead aVR may also prove helpful

The P wave of Lead 2 of the electrocardiogram is normally a blunt rounded sometimes slightly notched or scalloped upright deflection 1 to 3 mm high (each millimeter represents in a properly standardized record one tenth of a millivolt) and not over 0 1 second wide at the lower border of the baseline between corresponding points of upstroke and downstroke This wave represents the spread of excitation over the atria along the muscle bundles from the normal starting point the pacemaker at the head of the sinoatrial node which lies at the junction of the superior vena cava and the right atrium (Figure 39 page 183) The atrial electric axis which is the resultant of the spread of current in all directions over the muscle of right and left atria is normally directed down and to the left in its projection on the anterior plane of the body which is that represented by the routine electrocardiogram The P wave itself is very short in time interval and represents only about one third of the duration of atrial systole it is followed however by a slight change in baseline of varying extent usually directed downward coinciding in time with the rest of the atrial systolic interval but as a rule concealed by the superimposition of the first ventricular complex or QRS wave In heart block this late evidence of atrial electric activity may sometimes be clearly seen It has been called the atrial T wave or Ta deflection (Figure 53)

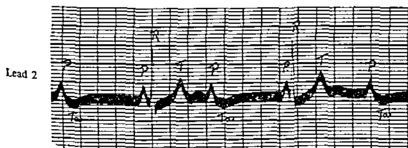


FIG 53 Electrocardiogram showing Ta waves in complete heart block Lead 2

The P wave of Leads 1 and 3 In Lead 1 the P wave is called P_1 It is of lower amplitude normally than in Lead 2 sometimes it is flat or isoelectric and so may be invisible rarely it may be greater than the P wave in Lead 2 (P) normally when the P wave of Lead 3 (P_3) happens to be inverted Very rarely the P wave may be inverted in Lead 1 when there is normal rhythm such a finding means congenital dextrocardia if an error has not been made in the attachment of the electrodes with resulting totally upside down Lead 1 When P_1 is 2 mm or more in amplitude it is abnormal and the same factors responsible for an abnormally high or wide P are also responsible for too large a P_1 In other respects too the discussion about P applies to P_1

In Lead 3 the *P* wave may normally be upright isoelectric diphasic or even slightly inverted It is therefore the least desirable of the three bipolar limb leads for study of the atrial complex However arrhythmias may be present in this lead and not in the others and one may also wish to note the character of the P_3 wave to aid in the interpretation of atrial abnormalities in the other leads and of the significance of inversion of T_3

In the *unipolar limb leads* the *P* wave like the *QRS* and *T* waves varies normally in direction and amplitude with the position of the heart In the right arm lead (aVR) it is almost invariably inverted and often closely resembles except for its direction the *P* wave of Lead 2 In the left arm and left leg leads it is upright and of variable height higher in aVL than in aVF if the heart lies horizontally and vice versa if the heart is vertical

In the *unipolar precordial leads* V_1 to V_6 inclusive, the *P* wave is not usually so well marked as in the limb leads it may be of fair amplitude however and more often upright than otherwise in the first position just to the right *of the sternum and when the right arm is used as the indifferent or distal lead* point in general it may be upright, isoelectric diphasic or inverted

Abnormalities of the *P* wave The description of the *P* wave abnormalities herein refers in particular to Lead 2 which as a rule of the routine leads shows them best

The *P* wave may show abnormalities of size and shape whether the heart rhythm is regular or not Moreover the *P* wave itself may remain normal in some instances of irregular or disturbed rhythm as in heart block Disorders of rhythm will be considered in the last three chapters of the book Sinus arrhythmia however demands a brief discussion now

Due to a variable activity of the pacemaker in the sinoatrial node caused by vagal influence and often associated with some bradycardia sinus arrhythmia (Figure 161 page 927) is generally a simple waxing and waning of rate with the intervals between normal *P* waves first decreasing and then increasing in phases related to the corresponding phases of respiration inspiration and expiration It is a normal phenomenon most common in children If very marked or not related to respiration it is an abnormal phenomenon in which case digitalization or faulty coronary circulation or an unknown factor may be responsible The *P* waves may decrease in amplitude with the periods of bradycardia as the pacemaker descends along the sinoatrial node usually they do not so decrease

Increase in amplitude (height) of the P wave is usually associated with increase in its width or duration although one may be present without the other An amplitude of 3 mm or more and a duration measured between corresponding points of upstroke and downstroke at the baseline of over 0 1 second are greater than the normal measurements in the subject at rest Although exercise and sometimes increased sympathetic tone with tachycardia induced otherwise than by exercise tend to increase the height of the *P* wave even above the usual normal limit a constant increase in height or width or both of the *P* wave is most often found in three conditions namely mitral

stenosis and two congenital anomalies atrial septal defects and the tetralogy of Fallot both of which especially the first are associated with considerable atrial enlargement Hypertension especially with myocardial failure and less commonly other ill defined conditions may cause high *P* waves in the electro cardiogram When this atrial deflection is abnormally high or wide it tends also to be abnormally notched sometimes the notching is so deep that the deflection appears doubled Increased width of the *P* wave with or without increase in height is more likely to indicate enlargement of the left atrium as in mitral stenosis while preponderant increase in height with or without in crease in width is more often found with enlargement of the right atrium as in the case of a congenital atrial septal defect

Decrease in amplitude may occur in vagal depression of the sinoatrial node with probable displacement of the pacemaker from the head of the node down toward the tail and this may be halfway or more along the sulcus terminalis toward the inferior vena cava This change in *P* wave may be seen to occur gradually or suddenly or it may be a constant finding it is frequently asso ciated with a slowing of the heart rate It may sometimes be produced through vagal stimulation by pressure over the carotid sinus but it also may occur indirectly through the effect of digitalis or it may infrequently occur spon taneously as for example during the slowing of the heart rate at the end of expiration The clinical condition in which an abnormally low in fact often almost isoelectric or flat *P* wave is regularly found is hypothyroidism (Figure 92 page 454) due to either myxedema or cretinism This smallness of the *P* wave in such cases accompanies a tendency to low voltage throughout the electrocardiogram particularly involving the *T* wave When the clinical con dition improves and the basal metabolic rate rises toward normal under treat ment with thyroid gland the *P* wave also becomes more normal Under other varied circumstances the *P* wave is occasionally found very low the reasons for which are not clear Heart failure alone does not cause the change

Absence of the P wave as a separate definite deflection results from several causes (1) In the first place this is most commonly due to atrial fibrillation in which orderly sequence of atrial contraction is replaced by irregular rapid incoordinated atrial movement (see Chapter 33) (2) In the second place the *P* wave may be replaced by regular instead of irregular baseline oscilla tions due to another condition closely related to atrial fibrillation namely atrial flutter (see Chapter 33) (3) In the third place the *P* wave may be partly or wholly buried in the *QRS* wave or in the *T* wave in cases of atrio ventricular block (Figures 53 and 164 page 935) of paroxysmal tachycardia (Figures 156 and 157 pages 879 881) and of premature beats whether of atrial or ventricular origin (Figures 154 and 155 pages 868 869) of reciprocal rhythm or ventricular escape (Figure 161 page 927) and finally of the rare atrioventricular nodal rhythm (Figure 163 page 932) In most instances of these abnormal rhythms the *P* wave does not exactly coincide either with the *QRS* wave or with the *T* wave and so it can be distinguished A mechanical tracing of the jugular pulse may in some of the obscure cases reveal what is

going on by the presence or absence of the *a* wave superimposed on the or on the *v* (4) Finally true atrial standstill or paralysis either transient complete may account for the absence of the *P* waves due to depression the pacemaker in the sinoatrial node and to inability of the lower, that is t atrioventricular node to start an atrial contraction (see Figure 162 page 979)

Inversion of the P wave (1) Inversion of the *P* wave in Lead 2 is abnormal and occurs most commonly in the case of atrial premature beats (see Figure 154) (2) Inverted or diphasic *P* waves also occur sometimes with continuous abnormal atrial rhythms most commonly in atrial paroxysmal tachycardia (Figure 156 page 879) (3) A third cause for inversion of the *P* wave very much rarer than that due to atrial premature contractions or to atrial paroxysmal tachycardia is atrioventricular nodal rhythm already mentioned (see Figure 163) Rarely an excessive irritability of the atrioventricular junctional tissue may give rise to paroxysmal tachycardia originating there (4) A fourth cause of inversion of the *P* wave is retrogression giving rise to a so called retrograde *P* wave following a ventricular premature beat

In some instances the *P* waves are more readily studied otherwise than in Lead 2 for example in the special atrial lead with exploring electrode in the third intercostal space at the right sternal border or in an esophageal lead when the *P* waves are indistinct or not seen in other leads

THE ATRIOVENTRICULAR OR *P R* (*P Q*) INTERVAL

The *P R* (*P Q*) interval is routinely studied in Lead 2 but observations of its length in the other leads should always be made It is a measure of atrioventricular conduction time from the atrial pacemaker through the atrial muscle across the junction from the atrial myocardium to atrioventricular node through this node and the bundle leading down from it and through the right and left bundle branches and their ramifications in the Purkinje network into the ventricular muscle fibers themselves at which moment the *QRS* wave begins The *P R* interval is measured from the beginning of the upstroke of the *P* wave to the beginning of the *QRS* wave whether this be upstroke or downstroke It normally varies in the adult from 0 12 to 0 20 (or even in rare cases 0 21 or 0 22) second averaging 0 16 second and in infancy and childhood from 0 08 to 0 18 second averaging 0 12 or 0 13 second Its duration is undoubtedly a function of the heart size (Figure 53 page 207)

Some years ago it was demonstrated (White Leach and Foote 1941) that an error may arise in the measurement of the *P R* interval especially in Lead 2 due to the neutralization of *Q* and *R* waves in two of the three classical leads with resulting isoelectric onset of the *QRS* waves in the other lead thus apparently prolonging the *P R* interval This happens most commonly when a short *Q* or *R* in Lead 1 is exactly equal in amplitude and duration to a short *R* or *Q* in Lead 3 the *P R* interval in Lead 2 is then abnormally prolonged by 0 02 or 0 03 second to include the isoelectric onset of *QRS* Or

otherwise Q_1 may neutralize Q to prolong $P R_3$ or Q_3 may neutralize Q to prolong $P R_1$ In occasional cases this error is clinically important when a $P R$ interval of 0 19 or 0 20 second is read as 0 22 second Hence careful scrutiny for this possible error is always essential A factor less important, which may erroneously shorten the P-R interval or neutralize the other effect is an isoelectric beginning of the P wave

Lengthened P R interval If the $P R$ interval is over 0 21 second atrioventricular block is said to be present Only very rarely is a $P R$ interval found to measure normally over 0 20 second but in a few normal adults it has apparently even reached 0 22 second The greater part of the $P R$ time interval is consumed in the passage of the excitation wave through the atrioventricular node and the atrionodal junction just above it (see Chapter 34) The commonest causes of prolongation of the $P R$ interval are active rheumatic myocarditis coronary heart disease and digitalis intoxication

Shortened P R interval The $P R$ interval may frequently appear shortened when the atria and ventricles are beating independently as in complete heart block reciprocal rhythm or ventricular escape and in many instances of the ventricular premature beat In such cases it is better to speak of the intervals between the P waves and the R waves rather than of the $P R$ interval as such True shortening of the $P R$ interval is found in atrioventricular nodal rhythm when the P wave almost always inverted falls just before just after or with the R wave and in that variation of normal rhythm which consists of wide *QRS* waves with shortened $P R$ intervals (of 0 1 second or less) in healthy young persons prone to paroxysmal tachycardia (Wolff Parkinson and White 1930) (see Figure 168 page 953 and Chapter 34)

THE FIRST VENTRICULAR DEFLECTION OR *QRS* WAVE

The normal *QRS* wave The *QRS* wave the first ventricular deflection of the electrocardiogram and sometimes called for short the R wave is in *Lead 2* a sharp spike like monophasic diphasic or triphasic complex with little or no initial downward projection known as the Q wave a high upward projection known as the R wave and a variable usually slight to moderate downward projection called the S wave (Figures 40 42 43 and 44) Together all components of the *QRS* complex should measure not over 0 1 second in duration This first ventricular complex (*QRS* wave) represents the rapid activation of the entire ventricular myocardium by the excitation wave as it leaves the end branches (called the Purkinje fibers) of the special intraventricular conducting mechanism below the bundle of His The terms dextrogram and levogram have been applied to records representing in experimental animals the primary spread of the excitation wave through right and left ventricles respectively the addition of dextrogram and levogram results in the record obtained from both ventricles simultaneously For the sake of convenience and uniformity it has been agreed generally to call the first upward deflection of the *QRS* wave the R phase or wave any downward deflection

preceding the *R* the *Q* wave any downward deflection following the *R* the *S* wave and a second upward deflection following the *S* the *R* wave, if there is but one deflection downwardly directed it is labeled the *QS* wave (Committee of Electrocardiographic Nomenclature American Heart Association 1943) So far as time relations are concerned the *Q* of Lead 3 may coincide with the *R* of Lead 1 and the *R* of Lead 1 with the *S* of Lead 3 the nomenclature is not concerned with time relations but rather with direction above or below the baseline

The *Q* part of the *QRS* complex in *Lead 2* is usually absent or at most but a short point projecting 1 or 2 mm below the baseline except in the case of infants and young children when it may form a more appreciable part of the whole *QRS* complex being as great as 3 or 4 mm in amplitude The *R* wave in Lead 2 in the normal adult varies from 5 to 35 mm in amplitude and in infants from 5 to 10 mm It is sharp rarely slightly notched or slurred on upstroke downstroke or peak It may be the only part of the *QRS* complex present The *S* wave is usually but a slight sharp downstroke of 1 to 3 mm immediately succeeding the *R* wave in fact continuous with it, it is frequently absent

In *Leads 1 and 3* the *QRS* waves have normally less amplitude than in Lead 2 When the *R* or *S* wave occurs alone it is probable that either the other components are fused with it or they may be isoelectric and therefore invisible in one or another lead thus resulting in an erroneous measurement of the *QRS* duration A narrow *QRS* wave with isoelectric onset ending or both is most commonly found in Lead 2 where its apparent duration may in rare cases measure only half that of QRS_1 or QRS_3 an important error especially in the presence of bundle branch block which may be clearly evident in Leads 1 and 3 Thus all three leads must be carefully scrutinized not only to determine the correct measurement of the *P R* interval but also to learn the true *QRS* duration the widest *QRS* wave in any one of the three classical leads is the correct one and so as a rule, is the shortest *P R* interval Frequently in Lead 3 but rarely in Lead 1 the phase of the *QRS* wave with the greatest amplitude is normally directed downward whether *Q* or *S*

In the *unipolar limb leads* (Figures 42 43 and 44 pages 190 191 192) the *QRS* wave is normally inverted in Lead aVR with deep *Q* and small *R* usually upright but sometimes inverted (if the heart is very vertical) in Lead aVL and rarely normally inverted that is with *Q* wave in Lead aVF there may be very small *R* and *S* waves in Lead aVF if the heart lies horizontally

In the *six unipolar precordial leads* (V_1 to V_6 inclusive) the *QRS* wave is normally diphasic with short *R* and deep *S* in the first two leads and tall *R* and short *S* in the last two leads with *R* and *S* of intermediate amplitudes in Leads V_3 and V_4 in other words the *R* wave increases and the *S* wave decreases as one moves from right to left (see Figures 42 43 and 44 pages 190 191 192) It is to be noted that in the precordial leads the peak of the *R* wave marks the time of arrival of the intrinsic excitation wave at the muscle under

lying the particular exploring electrode involved the larger the ventricle the later and the higher the peak while the *S* wave usually reflects the activity of the opposite ventricle *Q* waves normally are absent or small Hence since the left ventricle is normally preponderant in size the *S* waves are larger over the right ventricle (that is in the right precordial leads) and the *R* waves are larger over the left precordial leads However the position of the heart enters in and may cause on occasion a very confusing picture especially if we take into account rotation of the heart around each of its three axes (Goldberger 1947) The effects of these variations of position added to the effects of disease processes and of various physiologic and toxic states comprise an extremely complicated miscellany that will require much research completely to elucidate

Abnormalities of the *QRS* wave The *precordial leads* may show the state of different parts of the heart in particular of the right and left ventricles better than do the limb leads since they reflect in the main what is directly beneath them Thus if the right ventricle is enlarged there is a delay in the appearance of the intrinsic deflection represented by the peak of the *R* wave in Leads V and V_2 overlying the right ventricle and along with this delay frequently an increase in amplitude also If there is right bundle branch block the intrinsic deflection is still further delayed in those leads resulting in a wide bifid or M shaped complex Also if the right ventricle is enlarged there tends to be a large *S* wave in the left precordial leads over the left ventricle that is in Leads V and V_6 Either Lead V_3 or V_4 is often a transitional point sometimes directly over the interventricular sulcus and sometimes over either ventricle and at right angles to the spatial axis as such either one is commonly used in identifying the anteroposterior plane in vectorcardiography (see page 202) In obscure cases x ray examination and the limb leads can help a good deal

If the left ventricle is enlarged the *QRS* waves in Leads V_5 and V_6 are altered accordingly with delay in appearance of the peak of the *R* wave (intrinsic deflection) higher amplitude of the *R* wave and in Leads V and V_2 over the right ventricle increased *S* waves Here again displacement or rotation of the heart to the right gives much more evidence of the left ventricle in the precordial leads than usual and may be misleading In left bundle branch block there is a much delayed intrinsic deflection peak in Leads V and V_6 often giving an M shape

The enlargement of the heart that affects the precordial *QRS* wave especially is that due to hypertrophy dilatation also has an effect on the duration of the *QRS* wave but manifests itself more on the *S T* segment and *T* wave because of the abnormal myocardial condition

It is also important to note that normally the bigger the heart the wider the *QRS* wave without the need of postulating any abnormal delay in i v conduction Thus the human infant s *QRS* wave is but 0 05 second wide normally the human adult s 0.10 second while the normal adult elephant s *QRS* wave is 0 20 second in duration (Figure 54) it would seem likely that the adult whale s *QRS* wave should be 0 4 second wide Thus hypertrophy alone

undoubtedly gives rise to slightly increased *QRS* duration even up to 0 1? second without bundle branch block per se

Absence of the R wave leaving only a QS complex is an important residual effect of a myocardial infarct underlying the particular precordial lead concerned This finding when present is a significant clue differentiating myocardial infarction from other conditions that may produce abnormal precordial *T* waves

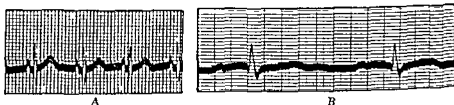


FIG 54 (*A*) Electrocardiogram (Lead 2) of a normal newborn infant B B showing the very short time intervals *P R QRS* and *Q T* (*B*) Electrocardiogram of a normal middle aged elephant M showing the very wide time relations a function of the size of the elephant s heart in contrast to the time intervals of the infant s electrocardiogram The speed of the film is the same in both (*A*) and (*B*)

An important observation that should be added concerns the amplitude of the *QRS* wave in the precordial leads Of equal importance with actual ventricular size is closeness of the lead to the heart Thus a thin chest wall will result in greater amplitude while a thick (e g obese) chest wall or fluid will decrease the amplitude

In the *unipolar limb leads* position of the heart is particularly reflected in the *QRS* waves as well as is heart disease In general a deep *S* wave in Lead aVR goes with left ventricular preponderance and a horizontal heart position while a high *R* wave in Lead aVF goes with left ventricular preponderance and a vertical heart position a *Q* wave is normally encountered but rarely in Lead aVF and an absence of *R* wave means a serious myocardial defect (an electrical hole facing the lead point usually due to infarction)

Finally in the old classical bipolar limb leads despite the concentration of interest in these leads in earlier editions of this book little can really be said about abnormalities of the *QRS* waves because of the wide range of the normal and the striking effect of varying positions of the heart Thus the great bulk of instances of so called right and left axis deviations is of physiologic interest only associated primarily with heart position although there are cases of course, of extreme degree of really significant axis deviation as in the case of the tetralogy of Fallot or of the atrial septal defect Also deep *Q* waves in Lead 1 are abnormal usually signifying anterior myocardial infarcts and especially prominent *Q* waves in Leads 2 and 3 generally mean posterior myocardial infarcts And of course *QRS* waves over 0 12 second wide mean bundle branch block but it is not always so easy as we used to think to tell right from left branch blocks in these leads alone There are exceptions that are properly revealed only in the precordial leads which should always be

taken anyway in cases with widened *QRS* waves As a rule it is true that wide upright *QRS* waves in Lead 1 and wide inverted *QRS* waves in Lead 3 mean left bundle branch block the reverse being true for right bundle branch block The last chapter in the book will have more to say about this

The term *low voltage* has been applied to the *QRS* wave in particular when it has extremely small amplitude either above or below the baseline At one time 5 mm that is 0 05 mv was arbitrarily selected as the borderline of normal Inasmuch however as normal individuals have shown amplitudes either above or below the baseline of the limb leads of 4 to 5 mm (0 4 to 0 5 mv) it is better to restrict the term low voltage to amplitudes of the *QRS* wave of 3 mm (0 3 mv) or less especially if the low voltage involves the *T* and *P* waves too Such low voltage has been noted in several conditions in particular in cases of diffuse myocardial disease due to coronary atherosclerosis or other cause extensive pericarditis acute or chronic and rare factors as yet unexplained In such cases the precordial leads generally show fair amplitude of the *QRS* waves but in a few instances they too may be much reduced and when they are the causative abnormal conditions are usually of greater degree The voltage however of the *QRS* waves in the precordial leads is affected also by distance of the electrode from the heart Thus an extensively fat chest wall or much fluid or air interposed between the heart and chest wall are factors that reduce the precordial *QRS* voltage

Alternation of the amplitude of the QRS waves without other change (that is without alternating change of shape or of time interval) is exceedingly rare I have seldom encountered it in the past 30 years A few years ago two cases were reported the first case being the only one found in a series of approximately 10 000 electrocardiograms taken over a period of 13 years (Hamburger Katz and Saphir 1936) the prognosis is apparently bad as in the ca e of the ordinary pulsus alternans On the other hand alternation of the arterial pulse is common and is attended in only the rarest cases by electrocardiographic alternation either of *QRS* waves or *T* waves or both

THE *S T* SEGMENT

Immediately following the onset of systole that is after the *QRS* wave there is usually in the normal subject a short isoelectric interval showing itself electrocardiographically as the *S T* segment following the *S T* junction Both the segment between the *S* and the *T* waves and that of the *T* wave itself are easily susceptible to modifying influences physiologic effects structural changes anoxia and myocardial infection and poisoning which may produce changes of shape and amplitude The *S T* segment and the *T* wave represent simply phases of the same electric process repolarization during cardiac systole The *S T* junction and *S T* segment may be normally slightly elevated up to 1 mm in limb leads and to 2 mm in precordial leads

Changes in the S T segment There are frequent changes in the *S T* segments which accompany abnormalities of the *T* waves themselves but which

actually may be more important in the information they yield about the myocardium they are as a rule temporary however subsiding when toxic influences and currents of injury subside The most common and most striking S T segment abnormalities are those associated with digitalis intoxication and with myocardial infarction and ischemia (most commonly from coronary disease rarely from trauma or a state of vascular shock or anoxia) acute pericarditis with its associated subpericardial myocardial involvement may elevate the S T segments appreciably especially in Leads 1 and 2 and in the precordial leads involved With full digitalization the S T segment of Leads 1 2 and 3 and of the multiple precordial leads is considerably depressed and is said to sag dropping sometimes several millimeters below the base line so that the T may arise very low and be diphasic or in extreme cases totally inverted (see Chapter 30) This digitalis effect is in contradistinction to the findings in acute myocardial infarction and ischemia when the S T segments are depressed or raised from the baselines in the opposite direction to the T wave changes that is early in the anterior wall type of infarction the S T segment is elevated in Leads 1 V_4 and V and depressed in Lead 3 and vice versa in posterior wall infarction type these changes are transient, persisting as a rule but a few hours or days (see Chapter 21) The S T segment tends to be markedly elevated in the multiple precordial leads over the region of the fresh anterior infarct while it may be considerably depressed in cases of acute posterior infarction (see Chapter 21) Also injury at the endocardial surface of the left ventricle may cause depression of the S T segments in the precordial leads over the left ventricle in contrast to the effect of the more usual subpericardial lesions In the case of large chronic myocardial infarcts usually associated with cardiac aneurysms the S T segments may be permanently displaced (e g elevated in Leads 1 V_4 and V_6 in the case of large anterior aneurysms)

Infectious changes other toxic poisoning of the myocardium and hyperventilation may sometimes affect the S T segment but rarely as much as does acute infarction or digitalization hypothyroidism has but little effect on the S T segment while flattening out the T waves In some cases of left ventricular enlargement (or strain) there is a slight depression of the S T segment in Lead 1 even when there is no left axis deviation (Barnes 1940) In fact it is now well recognized that S T segment depression in Lead 1 and in Leads V_4 and V is more characteristic of the effects of strain on the left ventricle than is left axis deviation this simulates the effect of anoxia in acute coronary insufficiency

THE SECOND VENTRICULAR COMPLEX OR *T* WAVE

The normal *T* wave The *T* wave or second ventricular wave of the normal electrocardiogram is in Lead 2 a blunt rounded upright deflection following the S T segment beginning gradually from the isoelectric baseline a short but variable distance about 0 05 to 0 15 second after the end of the QRS wave rising to a height of 2 to 10 mm usually 3 or 4 and sloping somewhat more

sharply downward to the baseline again to end about 0 25 to 0 30 second after the end of the normal *QRS* wave (Figures 42 43 and 44) The duration or width of the *T* wave thus varies greatly from about 0 10 to 0 25 second It falls during ventricular systole ending with the end of systole and the occurrence of the second heart sound It has been variously explained probably best as the repolarization (recharging) of the myocardium as contrasted with the depolarization (electric discharge) of the myocardium represented by the *QRS* wave The *T* waves in Leads 1 and 3 are normally of less amplitude as a rule than the *T* wave T_1 is low (about 1 or 2 mm) but almost invariably upright normally while T_3 also of low amplitude may be normally upright flat, or even inverted The *T* waves in the unipolar limb leads vary from normally inverted in aVR to upright or inverted in aVL and aVF depending on the position of the heart tending to be inverted in aVL and upright in aVF in the case of a vertical heart and upright in aVL and low but not inverted in aVF in the case of a horizontal heart The *T* wave in precordial Leads V_3 to V_6 inclusive is almost always upright (about 3 to 6 mm) in the normal adult but in the young child it may be inverted normally The *T* waves vary from very low flat or inverted in V_1 with increasing amplitude to high (5 to 10 mm) in V_3 and V_4 to lower levels in V and V_6 they should not normally be inverted in the adult except in V_1 and V

Physiologic variations of the T wave As stated above the *T* waves in Lead 3 normally vary widely from upright to inverted depending in large part on position of the heart as affected by the height of the diaphragm in opposite phases of respiration and in opposite body builds thus in full inspiration and in the case of a vertical heart the *T* waves in Lead 3 tend to be upright in direction with a swing of the electric (and anatomic) axis toward the right while in full expiration and in the case of a horizontal heart the *T* waves in Lead 3 tend to be inverted with a swing of the axis toward the left (see Figure 4 page 33)

Until recent years however flattening or inversion of the *T* waves in Leads 1 2 and V_3 to V_6 in the adult has been attributed to actual heart disease In Leads 1 and V_4 and V such a surmise is almost invariably correct so far as we yet know with very rare exceptions due to the same factors namely heart position and autonomic nerve influences which can be responsible in the case of the far more numerous exceptions found in Lead 2

Occasionally flattening notching or even inversion of the *T* waves in Lead 2 may be a positional effect in normal individuals in such cases a vertical heart position in a long thorax with tendency to right axis deviation is attended in the sitting or standing position by notched diphasic or inverted *T* waves which assume the usual normal upright appearance in the recumbent position or on deep expiration (with or without much of any change in axis deviation of the *QRS* waves on changing position rotation of the heart probably playing the important role) It is important to recognize this normal variation which has frequently in the past been attributed to myocardial disease (see Figures 5 and 6 page 34 and page 35) (White Chamberlain and Graybiel 1941) In very rare cases even T_1 may be normally inverted when the heart is

unusually placed vertically with the T in aVL deeper than in aVR or horizontally with marked clockwise rotation

In addition to the effect of position autonomic nerve impulses may affect the T waves in Lead 2 Sympathetic stimulation as *during* exercise and from fear or adrenaline and vagal inhibition as from atropine lower the T waves even to the point of inversion (Figure 55) (Hartwell et al 1942), while

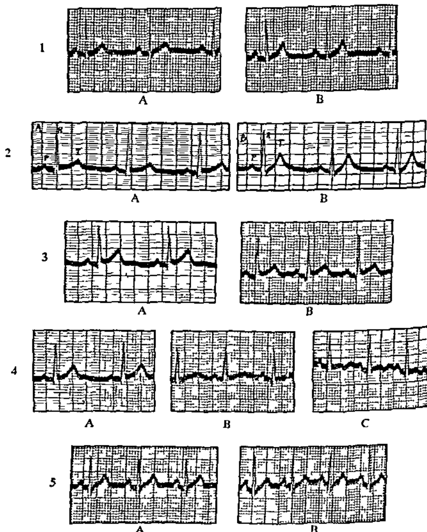


FIG 55 Changes in the T waves of the electrocardiogram resulting from the action of certain drugs in particular ergotamine atropine and adrenaline and of exercise (during and after) Note the increase in the T waves by vagus stimulation as evidenced by (1) the action of ergotamine and (2) the after-effect of exercise and the depression of the T waves as the result of sympathetic nerve stimulation or preponderance as evidenced by the effect of (3) atropine (4) adrenaline and (5) exercise itself directly All tracings are of Lead 2 (A) control record (B) records at height of effect (C) shows maximal adrenaline effect—drug given intravenously (Hartwell Burrett Graybiel, and White *J Clin Investigation* 1942 XXI 409)

vagal stimulation as from ergotamine and *after* exercise raises the T waves (Figure 55)

Abnormalities of the T wave *Increase in amplitude of the T wave* The end of the T wave of Lead 1 tends to become higher in cases of posterior myocardial infarction due to coronary thrombosis in contrast to late inversion of the T wave in Lead 3 while the reverse is true that is there is a late increased elevation of T_3 when there is late inversion of T_1 in the cases of anterior wall infarction In the old Lead 4 and in the multiple precordial leads over the left ventricle V_4 V and V_6 the T may remain unchanged or become higher than normal in the posterior wall infarction it is almost always considerably inverted in the anterior wall infarction (see Chapter 21) especially in chest Leads V_4 V and V_6 In cases of lateral wall infarction it may be inverted in Lead V_6 only

In the electrocard ograms of premature beats marked axis deviation and bundle branch block the S T segment and T wave are usually widely deviated from the baseline in the opposite direction from that of the abnormal QRS wave thus giving sometimes very high T waves A similar opposite direction of T wave from QRS wave in Leads 1 and 3 helps to separate the marked axis deviation due to pathologic cardiac conditions from left axis deviation of lesser degree which may be due to change in position of the heart (when the T wave tends to take the same direction from the baseline as does the QRS wave) Thyrotoxicosis sometimes stated to show a T wave increase is as a matter of fact generally without appreciable effect or has an opposite effect even to flatten or invert the T wave doubtless due to the sympathetic overstimulation

Decrease in amplitude and inversion of the T wave Decrease in amplitude of the T waves from the normal and their inversion in disease are found under several conditions In Lead 2 decrease in amplitude is frequently present in marked left or right axis deviation or even in right or left bundle branch block along with a diphasic character of the QRS wave due to the neutralizing effect of Leads 1 and 3 on each other In general however flattening and inversion of the T waves in the three classical leads are most commonly the result of digitalis action of myocardial ischemia or infarction from coronary disease of acute pericarditis or chronic constrictive pericarditis of infectious myocardial involvement and of hypothyroidism (myxedema or cretinism) There are differences between the effects of these five clinical conditions In the multiple precordial leads the T waves vary according to the part of the heart affected but are influenced like the limb leads by general factors such as digitalis myocarditis and myxedema

1 Digitalization usually causes a decrease leading to flattening or even in extreme cases to deep inversion of the T wave following a sagging of the S T segment (see Figure 158 page 897 and Chapter 30)

2 The T wave of myocardial ischemia or infarction due to coronary disease or insufficiency tends to be flattened or inverted in Lead 2 but varies in the other leads according to the site of the maximum amount of myocardial

change It is at first slightly elevated along with the $S\,T$ segment, in Lead 1 with or without very slight late inversion (Pardee s sign Pardee 1920) during the most acute stage of anterior wall type of myocardial infarction (due probably to a current of injury at the left ventricular apex) but it becomes usually sharply inverted after a few days remaining inverted for weeks, months or years When there is chronic coronary insufficiency with or without actual old infarction involving a large area of the left ventricle toward the apex the T waves in Leads 1 and V_4 and V_5 are usually flattened or inverted in their terminal portions In cases of anterior wall myocardial infarction or left ventricular basal ischemia the same statements just made concerning T_1 apply to the T waves in Lead 3 instead In the multiple precordial leads the T waves are unchanged or heightened in the case of the posterior wall infarction or left basal ischemia and flattened or inverted (often deeply so) over the left ventricle in the case of anterior infarction or left apical ischemia When there are multiple areas of infarction or ischemia there are multiple effects on the electrocardiogram which are often confusing perhaps the simplest combination is inversion of the T waves in Leads 1 2 and 3 with diphasic T waves in the precordial leads over the left ventricle when there are comparable infarcts at both apex and base (see Chapter 21)

In the multiple precordial leads inversion of the T waves over the right side of the precordium and not over the left indicate enlargement of or damage to the right ventricle or infarction of the interventricular septum while inversion of the T waves over the extreme left side of the precordium indicate infarction or other damage of the lateral wall of the left ventricle

3 With pericarditis especially when there is acute or chronic constriction of the heart and great vessels the T waves tend to become flattened or more often inverted in all leads after temporary elevation of the $S\,T$ segments but especially in Leads 1 and 2 for some days in the early stages (see Chapter 27)

4 With serious infections there are occasionally observed changes in the T waves consisting of decrease in amplitude flattening or inversion in both limb leads and multiple precordial leads similar to those just recounted as sometimes occurring in pericarditis these changes are due to acute myocardial involvement and are particularly likely to occur in rheumatic fever diphtheria and pneumonia and sometimes in virus diseases The same effects are due rarely to noninfectious poisons (other than digitalis which has been mentioned above) as from tobacco (see Chapter 23)

5 The T waves of hypothyroidism are very low absolutely flat (most commonly) or even inverted in all leads they resume a normal amplitude after thyroid therapy (see Chapter 18)

There are other rare instances of depression or inversion of the T waves of uncertain or unknown nature and even an individual who is apparently normal may temporarily show this finding due as a rule to unusual heart position or nerve influence (see Figures 5 page 34 and 55 page 218 for example)

The *T* wave is frequently diphasic but rarely notched Its diphasic character results often from the inverted nature of the *S T* segment which merges into the slightly upright *T* wave as in digitalis action occasionally the diphasic sequence is the reverse first upright then inverted as in cases of cardiac infarction A late notch or dip in a low *T* wave in Lead 2 suggests the effect of heart position in an otherwise normal person in the sitting position in such a case a further electrocardiogram should be taken with the subject recumbent or in full expiration to correct the effect of the heart s unusual angle or rotation

Alternation of the T waves in amplitude alone like alternation of the *QRS* waves is very rare it may accompany alternation of the arterial pulse as a serious sign

THE *Q T* DURATION

The time interval from the onset of the *QRS* wave to the end of the *T* wave can be taken to measure quite accurately the duration of ventricular systole when the deflections are clearly marked so that the end points are readily seen With good technic this so-called *Q T* duration of the electrocardiogram is the best measure we possess for the length of systole With clear curves measurement by the Lucas comparator gives an error under 0 01 second The *Q T* duration (duration of systole) varies primarily with the heart rate being shorter with faster rates and longer with slower rates about 0 35 second at a heart rate of 75 0 25 second at a rate of 120 and 0 45 second at a rate of 45 The *Q T* duration varies abnormally only in some cases with high grade atrioventricular and intraventricular block in ventricular premature beats in hypocalcemia and hypopotassemia and with marked enlargement (especially dilatation) of the heart in which conditions it is longer than the outer limit of the normal in heart failure a prolonged *Q T* duration (systole) is shortened by an adequate digitalis effect With respect to heart size it is of considerable interest that the duration of systole (the *Q T* duration) of the elephant s heart is relative to heart rate much longer than that of the human heart (White Jenks and Benedict 1938) (Figure 54 page 214) and one might justly prophesy that the whale s *Q T* duration like other time intervals would be similarly relatively prolonged

THE *U* WAVE

Occasionally in Leads 1 and 2 and frequently in the precordial leads there occurs normally a slight upright deflection a small wave usually less than 1 mm high but sometimes higher immediately following the *T* wave and therefore appearing in early diastole (Figures 40 42 44 and 53) This is called the *U* wave Its significance is unknown but it is probably representative of some diastolic electric process in the myocardium since it is more evident after a high or deep *T* wave than at other times and since it tends to be inverted when the *T* wave is inverted The *U* wave is apparently of little clinical

importance except that it may be abnormally inverted when the T wave is upright and that it may be confused with the P wave or more commonly with the end of the T wave in which latter case it may be wrongly interpreted as a notching of the T such an error can be avoided by a measurement of the expected Q T interval at the heart rate recorded

Serial electrocardiograms In closing this chapter I would like to emphasize the great importance of serial electrocardiography Repeated records are often essential for the diagnosis of such acute conditions as myocardial infarction, acute pericarditis and the acute cor pulmonale Annual monthly weekly daily or even hourly records may reveal much more than any single electrocardiogram Also every young person while in good health should have a routine electrocardiogram taken for future reference just as he or she should also have a chest x ray film

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CHAPTER 10

OTHER METHODS OF EXAMINATION

INTRODUCTION

The patient's history, physical examination, electrocardiogram and roentgen ray study have been discussed in the earlier chapters of this book and have been roughly appraised in value as parts of the complete clinical examination in the order of about 45, 25, 15 and 10 per cent respectively. These percentages add up to 95, leaving the remaining 5 per cent to be divided up among all the other methods of examination which include the technic of cardiac catheterization and the testing of blood, urine, strength and endurance, vital capacity and other respiratory functions, blood flow, circulation rate, and work of the heart and of the pulse. Various other tests of less immediate or routine cardiovascular importance, such as the basal metabolic rate and sputum and gastrointestinal examinations, are not included in this chapter but are referred to later in appropriate chapters. Any one of these methods of examination may, however, uncover a vital clue, and so they must all be borne in mind and turned to at once in case of need. Many of the additional tests, such as ballistocardiography, the discussion of which has been transferred to a more appropriate chapter (Chapter 8), are of much academic interest and worthy of use in special investigations; a few may some day assume practical importance in clinical medicine related to the heart and great vessels. As a whole, however, at the present time the methods discussed in this chapter are infrequently of prime importance in cardiovascular diagnosis, although they may be invaluable in the execution of special research.

CARDIAC CATHETERIZATION

Forssmann, W. "Die Sondierung des rechten Herzens" ("Sounding the Right Heart") *Klin. Wchnschr.* 1928, VIII, 2085.*

* Shortly after the publication of this paper Dr. Forssmann's attention was called to an earlier publication on catheterization of arm veins in the human for the purpose of therapy (Bleichroder, Unger and Loeb, "Intraarterielle Therapie," *B. Klin. Wschr.* 191[illegible]). However, this earlier work apparently did not include catheterization of the heart per se and was not followed up by further research or application.

Following the successful investigations in the cadaver I undertook the first study in living man in the form of a *research on myself* Next I arranged in a preliminary test to have my right elbow vein punctured with a thick needle by a colleague who kindly placed himself at my disposition for this purpose I introduced then as in the case of the researches on the cadaver a well oiled ureteral catheter of 4 Charrieres thickness through a cannula into the vein The catheter allowed itself to be introduced very easily to a length of 35 cm Since going further seemed too dangerous to the colleague we stopped the investigation at that point even though I myself *felt* quite well *After a week I undertook a further investigation alone* Since a puncture of the vein with a thick needle on my own body was technically too difficult I made under local anesthesia a venesection in my left elbow and introduced the catheter without any resistance in its whole extent of 65 cm This length *appeared to me after measuring the surface of the body to* agree with the distance from the left elbow to the heart On introduction of the catheter I had during the procedure merely a feeling of slight warmth in the wall of the vein similar to the sensation after intravenous injection of calcium chloride On backward movement the catheter touched the upper and lower wall of the subclavian vein I then felt an especially intensive warmth behind the collar bone under the insertion of the sternocleidomastoid Simultaneously doubtless through the stimulation of the vagus branches I felt a slight tendency to cough

The position of the catheter I confirmed *in a Röntgen photograph* and observed the shadow of the catheter itself by means of a mirror held by a sister before the fluoroscopic screen (Translation by myself)

Thus in 1929 Forssman successfully catheterized his own heart by way of an arm vein Considered a bold and dangerous procedure at first it has in the last few years become a commonplace though still a delicate method of study of the right heart chambers and pulmonary arterial circulation particularly in congenital cardiovascular disease and in measurement of the pulmonary blood pressure a longfelt want now at last realized (Figure 56) It is very important wherever cardiac catheterization is carried out to establish a well trained team of workers to ensure proper technic and adequate recording such a team usefully includes cardiologist roentgenologist cardiovascular surgeon and physiologic technician It is well to record the blood pressure in the superior vena cava in the right atrium in the right ventricle and in the pulmonary artery and its main branches by Hamilton manometer or by the newly introduced *electromanometer (see Chapter 6) Samples of blood for* determination of oxygen content are taken similarly from these various sources to determine if possible the entrance of oxygenated blood through atrial septal defect ventricular septal defect or patent ductus arteriosus (see Chapter 13) The course of the specially modified ureteral catheter 100 to 125 cm in length can be followed fluoroscopically as it passes from one chamber to another or in abnormal hearts into left atrium or aorta and x ray films can occasionally be taken It is possible also to use such a catheter to explore

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Also Forssmann mentioned the fact that Christeller and Eisner had used Ung r s arterial method in animal experimentation Forssmann refers to th se two earlier communicat ons in a short statement in the *Klin Wchn chr* 19 9 VIII ?87

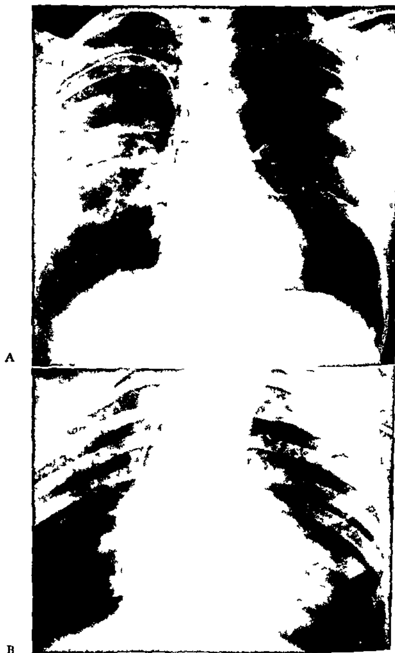


FIG 56 X ray films of thoraces with catheter in heart (*A*) Normal heart Catheter is seen entering the right atrium from the superior vena cava and its tip can be noted in the right pulmonary artery (*B*) Atrial septal defect with pulmonary stenosis The catheter is seen to pass from the right atrium through the septal defect to the left atrium and into a right pulmonary vein Note the lower position of the pulmonary vein in contrast to that of the artery



C

D

(*C*) Large patent ductus arteriosus The catheter is seen to pass from the main pulmonary artery through the ductus and down the descending aorta (*D*) Tetralogy of Fallot. The aortic arch is right-sided The catheter is seen entering the aorta from the right ventricle (Kindness of Drs Gordon S Myers, Massachusetts General Hospital Boston Bernard J Walsh Washington D C and Lewis Dexter Peter Bent Brigham Hospital Boston)

the coronary hepatic and renal veins and determine blood gases to study local organ metabolism Finally it is possible by the insertion of a special wire and electrode through the catheter to obtain right intra atrial and intraventricular electrocardiograms which as yet have been largely of academic interest (see Chapter 9)

In normal individuals the blood pressure in the superior vena cava has been found to be about 3 mm Hg in the right atrium 0 in the right ventricle 20 to 30 mm systolic and 0 diastolic and in the pulmonary artery 20 to 30 mm systolic and 5 to 10 mm diastolic With the catheter tip as far as possible in the pulmonary vessels an essentially capillary oxygen reading can be secured.

The oxygen content of blood samples taken from the superior vena cava and right atrium may vary considerably since the venous blood from various sources has not yet been well mixed For example a sample taken near the coronary sinus may have an oxygen content as low as 3 or 4 volumes per cent Mixing is more complete in the right ventricle and pulmonary artery where the oxygen content usually measures between 10 and 14 volumes per cent

Under abnormal conditions with congenital septal defects and patent ductus arteriosus there are increased blood oxygen contents in the right atrium right ventricle and pulmonary artery according to the position of the left right shunt pulmonary vascular involvement and certain heart conditions may elevate the pressure readings even to levels as high as three or four times the normal

TESTS INVOLVING THE USE OF RADIOACTIVE ISOTOPES

Cutting across various special fields of internal medicine and applicable to a variety of tests in such fields has been the introduction of radioactive isotopes in the years that have followed World War II Even in therapy also this newly acquired knowledge has played a role, particularly in the form of irradiated iodine to reduce the activity of the abnormal thyroid gland in thyrotoxicosis or of the normal thyroid in combating intractable angina pectoris or congestive failure (a medical thyroidectomy) But radioactive isotopes have played a role much more prominently in diagnosis and research than in therapy in cardiovascular disease In 1942 Hubbard et al used radioactive sodium to determine the velocity of blood flow in infants and young children This has been followed up since by Prinzmetal et al (1949) who have applied the method to adults In 1945 Nylin reported the determination of the circulating blood volume by the application of the new method worked out by Hevesy wherein blood corpuscles were tagged with radioactive phosphorus and the time of equilibrium of their dilution curves established by the use of the Geiger counter In normal cases the circulating blood corpuscles averaged 33 4 gm per kilogram of body weight while in heart failure there was a considerable increase with return to normal figures when the failure cleared in one case there was a drop of 28 per cent when congestion disappeared Using the same technic Nylin (1947 1948) has

studied the corpuscular and total blood volume in various organs including the lungs and the heart he found for example that 17 per cent of the total circulating blood volume was to be found in one lung and 13 6 per cent in the lower limbs Dow et al (1946) and Gibson et al (1946) used radioactive isotopes of iron similarly to measure the circulating red cell volume Prinzmetal et al (1947) studied the collateral circulation of the normal human heart by coronary perfusion with radioactive erythrocytes and glass spheres and later (1949) used a specially constructed ink-writing Geiger Mueller counter to record the passage of radioactive blood through the heart chambers which they called radiocardiography Burch et al (1947) have used radioactive sodium to study congestive heart failure and Smith and Quimby (1947) Elkin et al (1948) and Wright et al (1948) have used radioactive sodium to study the peripheral circulation

EXAMINATION OF THE BLOOD

Blood examination affords a wealth of data concerning its various constituents and properties which are sometimes of much value in the study of a patient with cardiovascular disease

Hemoglobin Usually the hemoglobin in cardiac patients is within normal limits 80 to 90 per cent by various methods (13 to 15 gm per 100 cc of blood) Slight anemia down to 70 or even 60 per cent hemoglobin may occur in severe or long-continued acute rheumatic heart disease Moderate to severe anemia down to 55 or even 40 per cent hemoglobin is sometimes present in subacute bacterial endocarditis although slighter grades are more common The discovery of a low hemoglobin content due to hypochromic anemia of noncardiac origin or to primary pernicious anemia may prove helpful in explaining not only systolic but also diastolic heart murmurs due to cardiac dilatation resulting from the anemia Sometimes the differential diagnosis between anemia secondary to bacterial endocarditis and that secondary to other factors is difficult An abnormally high hemoglobin content over 100 per cent is found with polycythemia resulting from congenital heart defects which are attended by cyanosis and a right to left shunt of blood This percentage of hemoglobin may be as high as 150 (22 gm) or more Polycythemia vera may in turn be itself a factor of circulatory strain (see Chapter 23)

Recently an iron pigment in muscle called myoglobin which like hemoglobin has a function of picking up and storing oxygen has been under investigation (Biorck 1948) but further study is needed to ascertain the clinical significance of variations of its amount in heart muscle

Red blood cells The red blood corpuscles are decreased below the normal in number relatively less than is the hemoglobin in the anemia of acute rheumatic heart disease and in that of subacute bacterial endocarditis as in almost any secondary anemia They usually vary between 3 000 000 and 4 000 000 per cubic millimeter according to the severity of the anemia rarely falling to 2 500 000 or 2 000 000 or below in the severest grades of anemia found in

bacterial endocarditis In contrast in the morbus caeruleus of congenital heart disease the red cell count is as high as 6 000 000 to 12 000 000

White blood cells *In infections of the heart the white blood* corpuscle counts are increased A slight leukocytosis with a total count of 10 000 to 15 000 per cubic millimeter and a polymorphonuclear percentage of 70 to 85 is common in acute endocarditis rheumatic or otherwise although frequently in mild cases the number of white blood corpuscles is normal in the more severe and fulminating cases of bacterial endocarditis with complications such as embolic infarcts it can be much greater even to a total white count of 30 000 with 95 per cent polymorphonuclear cells Cardiac infarction from coronary thrombosis or embolism usually results in polymorphonuclear leukocytosis for a few days from a slight degree (12 000 with 75 per cent polymorphonuclear cells) to a high degree (25 000 with 90 per cent polymorphonuclear cells) depending on the size of the infarct A small infarct may result in no obvious leukocytosis

Sedimentation rate The rate at which the sediment of nonclotted blood settles out is much increased in many disease conditions including the infections involving the heart (rheumatism bacterial endocarditis and tuberculous pericarditis for example) and myocardial infarction from coronary thrombosis It is a useful test not in differential diagnosis but in helping to determine when an active process has completely subsided particularly subacute rheumatism infectious activity in a constrictive pericarditis and active tissue replacement in myocardial infarction It is important to correct the sedimentation rate index for marked variations in the cell volume percentage (hematocrit) of the blood for example a fast rate of 0 5 mm per minute (in a 100 mm sedimentation tube with heparinized blood) in a case with severe anemia may be corrected to a normal rate of 0 25 mm per minute found when the hematocrit is normal (at 45 per cent) (Rourke and Ernstene 1930)

Blood culture Bacteriologic examination of the blood is occasionally helpful in endocarditis The smear shows no organism but a culture when enough blood 5 to 20 cc is taken and the culture medium hormone broth with a hydrogen ion concentration of *p*H 7 6 is carefully prepared should reveal the presence of the Streptococcus viridans in the great majority of cases of subacute bacterial endocarditis Sometimes several cultures must be taken before positive ones are secured At least three or four positive cultures are essential for complete confirmation of the diagnosis of subacute bacterial endocarditis one or even two positive cultures may be more or less accidental findings Cultures are also useful in determining the particular organism streptococcus staphylococcus pneumococcus gonococcus or rarer bacteria responsible for acute bacterial endocarditis Infrequently in rheumatic endocarditis streptococci have been found in blood cultures and sometimes are thought to be responsible for the infection but blood cultures positive for streptococci have similarly been found in various other diseases and even in relatively normal controls especially when there are chronic foci of infection particularly dental and immediately after tooth extraction (not particularly

after tonsillectomy) This finding is best interpreted as indicating that occasionally stray bacteria may invade the blood stream without causing disease except in rare hearts where there may be suitable soil for their growth as in the case of subacute bacterial endocarditis

Serologic reactions Although on rare occasions such serologic tests as those for the gonococcus or the echinococcus may be helpful if carefully carried out it is only the Wassermann or allied (Kahn or Hinton) reaction for syphilis that is of routine value Because of the relative infrequency of cardiovascular syphilis in certain communities this reaction will prove negative in most cardiovascular patients in those communities but in other parts of the world where syphilis is rife and its treatment inadequate a positive Wassermann reaction will be commonly found When it is positive the test is of help in confirming a diagnosis of cardiovascular syphilis made on other grounds or in calling attention to its presence When negative this test for syphilis is of only limited value although the great majority of all patients with cardiovascular syphilis (about 85 per cent) yield positive Wassermann or Kahn or Hinton reactions Even when positive the reaction may be misleading for nonsyphilitic heart disease and incidental syphilis may be present in the same patient also other conditions like jaundice and subacute bacterial endocarditis may rarely yield slightly positive reactions These facts must be remembered and great care and judgment exercised before a positive Wassermann reaction is allowed to influence diagnosis prognosis and treatment there may be a justifiable suspicion of cardiovascular syphilis but symptoms or signs are essential to establish the diagnosis

Viscosity of the blood Viscosity of the blood chiefly dependent on its cellular content is rarely an important factor so far as the circulation is concerned and its measurement is largely a matter of academic interest Occasionally however its increase as in high grade polycythemia where it may be as much as three times the normal is a distinct burden for the circulation and a threat for thrombosis it has to be offset in part by capillary dilatation Decreased viscosity occurs in anemia and temporarily in congestive failure or with forcing of fluid intake

Chemical analyses Certain chemical analyses of the blood have become of routine value in internal medicine including cardiovascular disease An excess of nonprotein nitrogen beyond the normal upper limit of 40 mg per 100 cc of blood or of urea nitrogen beyond 20 mg per 100 cc means nitrogen retention which in turn means renal insufficiency but usually not primarily renal disease in cardiac patients congestion from heart failure may be the cause An abnormal increase is an accompaniment also of uremia which may act to poison the heart and of a renal shut-down due to dehydration The amount of blood sugar normally not over 120 mg per 100 cc of blood is worth knowing when diabetes mellitus is suspected because of the frequent association of this disease with early arteriosclerosis and because of its unfavorable effect on heart disease but too low a blood sugar (as from excess of insulin) may also act harmfully in acute coronary heart disease

The serum content of albumin and globulin in relation to cardiovascular disease has not been shown to be of clinical importance in the differentiation of cardiac edema from the edema due to liver disease or to malnutrition Any one of these factors may complicate the others In heart failure the serum protein is usually normal in the other two conditions much lowered (to 5 0 gm per 100 cc or less) especially in its albumin fraction Although it is possible to measure the contents of various ions in the serum (e g , sodium—normally 136–145 meq per liter potassium—3 5–5 0 meq per liter calcium—9 0–10 5 mg per 100 cc and chloride—100–106 meq per liter), much still remains to be learned about the significance of the blood content of salts and their elements acid and base along with the hydrogen ion concentration which remains strikingly constant (7 35 to 7 45) through buffer action Suggestions of the significant effect that may result from abnormality of such relationships is shown however in an unusual elevation of the *T* waves of the electrocardiogram in acidosis and in the case of a high potassium content (which may also induce or favor the occurrence of heart block—Thomson, 1939) and depression of the *T* waves in alkalosis and low blood potassium as well as in the case of hypocalcemia (in tetany) in which with very low blood calcium (4 to 5 mg per 100 cc of blood) the duration of systole as measured electrocardiographically is prolonged appreciably beyond the normal dropping again within normal limits when the blood calcium is restored to normal (10 mg) It is also important to remember that the serum content of salts does not indicate the intracellular chemical status Finally there are other substances for which on occasion the blood should be analyzed e g cholesterol in coronary heart disease and thyroid diseases especially (normally 150 to 250 mg per 100 cc serum) and vitamins in suspected avitaminosis (A normally 40 to 100 units per 100 cc C normally 0 4 to 1 0 mg per 100 cc)

Oxygen in the blood The normal content of oxygen in arterial and venous heart blood measured in terms of percentage saturation (if all the hemoglobin were oxygenated the saturation would be 100 per cent) is 95 per cent saturation (18–21 volumes per cent) for arterial blood and about 70 per cent saturation (10–16 volumes per cent) for venous heart blood For certain parts of the body the venous blood will show a greater degree of unsaturation but this excess is neutralized in the venous heart blood by a lesser degree of unsaturation in other parts of the body Stasis of varying degree and increased tissue metabolism account for the differences The more active the metabolism and the greater the stasis anywhere the less oxygen remains in the blood and the bluer it becomes The dissociation of oxyhemoglobin however requires a favorable temperature and if the air is very cold so that the skin is chilled the peripheral skin circulation although greatly slowed gives not a blue but a red color due to the presence of unreduced oxyhemoglobin

A helpful instrumental device called the oximeter (Millikan 1932) for the photoelectric determination of blood oxygen saturation in man by standardization against known blood samples can be applied to the ear or even to whole blood via cardiac catheter

A decrease in amount of oxygen saturation of arterial blood can be of ˬ degree it has been found to be as low as 58 per cent in a case of our ¬ of congenital heart disease with the tetralogy of Fallot and marked cya- (Talbott et al 1941) 32 per cent in a cyanotic and fatal case of ˒ the influenza epidemic of 1918–1919 (Stadie 1919) and even per cent in a case of bronchopneumonia with increase to 79 per cent through oxygen inhalation (Meakins and Davies 1925) A decrease in oxy gen saturation of arterial blood is due to any one of eight factors as listed herewith (1) Pulmonary congestion from heart (left ventricular) failure may be so great that in the distended pulmonary capillaries much venous blood passes through without contact with the alveolar wall and the oxygen on the other side of that wall also moisture in the alveoli may prevent the proper entrance of air (2) Pulmonary vascular engorgement from mitral stenosis without real heart failure acts in the same way (3) Pneumonic or other consolidation which causes a shunt of venous blood to the left heart through the capillaries of solid lung into which little or no air and oxygen can penetrate may also reduce the oxygen content of arterial blood (4) Destruction of a large amount over half of the total lung tissue may prevent sufficient air from reaching the pulmonary circulation (5) Chronic emphysema and asthma in which the respiratory exchange is very limited may also prevent sufficient oxygen from reaching the alveoli and blood stream (6) High altitudes 10 000 ft (about 3 000 meters) and over where the oxygen content of the inspired air is low do not allow a completely normal oxygen saturation of the blood At 14 200 ft elevation the oxygen saturation of the arterial blood has been found to vary between 80 and 90 per cent instead of the normal of 95 per cent or slightly more (Barcroft and associates 1922) and at 17 500 ft the variation was from 67 6 to 84 6 per cent (average 75 per cent) in six resident healthy workmen (Talbott and Dill 1936) (7) Poisoning by carbon monoxide or other toxic agent to cause methemoglobinemia may prevent some of the hemoglobin from taking up oxygen in the lung (8) Congenital heart disease may be attended by shunts that is through atrial or ventricular septal defects large enough to allow a considerable amount of venous blood to cross directly into the arterial circulation without first going through the lungs Congenital transposition of the aorta and pulmonary artery may also be a cause

Three additional observations about blood oxygen are of interest In anemia where the hemoglobin is low in amount its saturation with oxygen may be normal and yet the total amount available for the tissues too little With polycythemia as in congenital heart disease the saturation with oxygen may be abnormally low and yet the total content—volumes per cent—be sufficient because of the increased number of red corpuscles Also some oxygen can be carried directly in the blood plasma without attachment to hemoglobin this is not a large amount but it is of some importance the ratio of oxygen so carried to that combined with hemoglobin being about 1 to 50

An increase of oxygen saturation of normal arterial blood can be but slight since it already averages about 95 per cent saturated but when there is oxygen

unsaturation inhalation of air rich in oxygen (for example 50 per cent) may restore the blood saturation to normal

A decrease of oxygen saturation of venous blood below the normal arises first from the various factors already enumerated for decrease of oxygen in the arterial blood The tissues in removing their quota lower the percentage still more sometimes to a level close to zero in marked stasis Two important factors are added by the peripheral circulation itself (1) increased tissue metabolism from activity and (2) stasis of the circulation These may simply be local phenomena but if they involve enough of the body a very appreciable decrease of oxygen saturation of the venous blood in the right heart will result.

An increase of oxygen saturation of venous blood in the heart above the normal may be found (even up to 94 per cent) when there is a congenital left to right shunt from left atrium to right atrium or from left ventricle to right ventricle or from aorta to pulmonary artery (via patent ductus arteriosus) as determined by cardiac catheterization or when the circulation rate is very rapid and the metabolic activity of the tissues slight as in paroxysmal tachycardia or it may be found locally when there is rapid circulation which does not give time for the usual oxyhemoglobin dissociation or when there is an arteriovenous aneurysm (anastomosis)

Carbon dioxide in the blood The carbon dioxide content of arterial blood is normally about 60 volumes per cent i e 60 cc of CO gas per 100 cc of blood (26–28 meq per liter milliequivalents per liter = volumes per cent divided by 2 2) The carbon dioxide is carried in the blood chiefly in the form of the dissociated acid sodium salt whereby the carbon dioxide is quickly taken up and given off If an excess of other acids appears in the blood stream as sometimes happens in diabetes or nephritis the carbonic acid radical is decreased by the blowing off of more than the normal amount of carbon dioxide in the lungs to maintain the normal blood and body reaction Or there may be a retention of alkali from the blood to neutralize acid in the body tissue with corresponding decrease in the carbon dioxide content of the blood In alkalosis the carbon dioxide content of the blood is increased

A decrease increase or normal amount of carbon dioxide may be found in the arterial blood along with an abnormally low oxygen saturation of this arterial blood though at first thought only an increase might be expected. This variability of carbon dioxide content is dependent on the relative influence of three factors (1) reaction of the blood whether acidotic when in heart failure there is a retention of bicarbonate in the tissues producing a lowered blood carbon dioxide value or alkalotic due to excessive vomiting with elimination of acid gastric juice or to excessive intake of alkalies causing an increased carbon dioxide content in the blood (2) pulmonary overventilation due to oxygen want resulting in a decrease of arterial blood carbon dioxide doubtless a factor in keeping this content low in heart disease and pulmonary underventilation of extreme degree as in very extensive pulmonary disease resulting in excess of arterial blood CO and (3) a shunt of venous blood into the systemic circulation as in marked congenital heart disease

sufficient to transmit blood with a high CO content The product of all these factors determines the carbon dioxide content of the arterial blood There may be a rise of arterial CO to as high a content as 85 volumes per cent (in a case of extremely marked pulmonary disease—emphysema and purulent bronchiolitis of the left lung with right lung collapsed by hydrothorax—Meakins and Davies 1925) It may fall to as low as 30 volumes per cent or less from diabetic or uremic acidosis or even from the effect of high altitude (27 volumes per cent in a subject at 14 500 ft elevation—Barcroft and associates 1922) the normal content averaging about 50 volumes per cent In heart disease with congestive failure and decreased oxygen content of the arterial blood the carbon dioxide content of the arterial blood is more often decreased than normal or increased The test of alveolar air carbon dioxide has long been used in estimating the degree of acidosis in disease but it is not reliable in certain pulmonary conditions as for example when edema of the lungs is present

A decrease increase, or normal amount of carbon dioxide in the venous blood may be found as in the arterial blood but there are two additional variable factors (1) speed of blood flow from arteries to veins and (2) activity of tissue metabolism If the blood flow is fast or the tissue metabolism decreased less carbon dioxide is delivered to the blood in the capillaries and the difference between the arterial and venous carbon dioxide content may be reduced from a normal average of about 3 volumes per cent to 1 5 or even 1 per cent if the reverse occurs the difference may be increased up to 10 volumes per cent

Thus in judging the results of blood gas analysis many things have to be taken into consideration including accuracy of technic The data may prove useful in helping to differentiate congenital heart disease with its shunts from acquired heart disease and in giving actual blood gas measurements for the degree of impairment of the circulation no matter what the cause The determination of the blood gases directly or by analysis of the alveolar air also permits an estimation of the blood flow that is of the amount of blood pumped by each ventricle per beat and per minute (see page 241)

Blood volume It is of some importance to distinguish between total [illegible] volume in any given person and circulating blood volume they [illegible] means synonymous It has been calculated that the circulating blood [illegible] in an adult of average size equals 5 to 5½ liters that is 3 liters per [illegible] meter of body surface or 80 cc per kilogram of body weight (Go [illegible] al 1935) The mean plasma volume measured by Evans blue [illegible] amounts to 45 to 50 cc per kilogram of body weight (Cohen [illegible] 1948) the volume of the circulating red blood cells has been [illegible] use of radioactive phosphorus (Nylin 1945) and iron (Dow [illegible] Gibson et al 1946) and found to average 30 to 35 gm per kilog[illegible] weight. Various blood depots will on occasion quite suddenly [illegible] considerable amount of blood from the active circulation to ho[illegible] for again by exercise or other requirement These normal bloo[illegible] lungs and systemic veins (especially in the splanchnic regio[illegible]

spleen Abnormal blood depots are most commonly varicose veins of the legs, which may on occasion (chiefly with a change to the standing position) so drain the circulation of blood that faintness or even syncope may occur Other abnormal blood depots are varicose veins elsewhere than in the legs lax abdominal vessels and large hemangiomata These blood depots are over loaded in congestive heart failure and the actively circulating volume of blood is also too great not only for the strength of the heart but in actual amount as well (Gibson 1941) there may be a real hydremia In vascular shock the circulating volume of blood is on the contrary reduced (see Chapter 30)

Available fluid volumes of the human body can be measured by the dilution of sodium thiocyanate injected intravenously The subtraction of the plasma volume and 70 per cent of the red cell volume from the total of the available fluid volume gives the available interstitial fluid volume (Morse et al 1947)

EXAMINATION OF THE URINE

Quantity Most important in a patient known or believed to have a failing heart or constrictive pericarditis acute or chronic are the determination and interpretation of the quantity of urine excreted compared to the fluid intake This should be done not for twenty four hour periods but for twelve hour day and night periods for both fluid output and intake in order to note delay in excretion as well as limitation or excess of flow These measurements must be made with a reasonable degree of accuracy and fluid excreted by stool also calculated if the bowel movements are watery We must not forget however that normally a considerable loss of water occurs in the expired air and that the sweat glands of the skin excrete water Normally there should always be therefore an appreciably larger intake of fluid than output of urine in twenty four hours by a few ounces (100 to 200 cc) at least and by a much larger amount where there is much perspiration Knowledge of the amount of urine alone is of little value unless this amount is excessively increased or diminished

If the systemic venous pressure is raised to a high level for a considerable length of time because of congestive heart failure so that fluid which has been distributed to the tissues at the arterial ends of the capillary loops cannot be wholly reabsorbed at the venous ends the output of urine is decreased relative to the fluid intake and also delayed beyond the normal If the osmotic pressure in the capillaries is much decreased because of low serum protein as in nephrosis and malnutrition fluid leaves the circulation in too large an amount and the urine output decreases In either case a decreased urinary output is often a good warning of an impending edema With the beginning of diuresis the amount of urine increases and approaches and often surpasses the fluid intake and edema if present begins to subside It is well to keep a chart of these two measurements routinely day and night in the case of a cardiac patient with congestive failure of any grade at all

Specific gravity The specific gravity of the urine is of less moment than the quantity but usually varies with it When the urine output is much decreased in congestive heart failure the specific gravity tends to be high due to concentration (1 025 to 1 030) but in spite of a slight to moderate albuminuria it is not so high as with a like degree of oliguria in health when the function of normal uncongested kidneys permits full concentration (1 030 to 1 040 or more) When there is a large flow of urine with diuresis the specific gravity usually varies very little and tends to be low under 1 010 If there is poor renal function especially in chronic nephritis the night amount tends to exceed that of the day and the specific gravity usually maintains a fairly constant figure

The urine concentration test of renal function systematically introduced by Volhard (1918) but simplified by Fishberg (see his fourth edition of *Hypertension and Nephritis* Lea and Febiger Philadelphia 1939 page 77) is the most practicable of the various functional tests of the kidney for routine use Briefly it is as follows On the day and night of the test the subject drinks no fluid after the noon meal eating a dry supper The urine passed during the afternoon and at bedtime is discarded as well as any during the night The first urine passed in the morning is saved in a bottle After an hour more in bed a second specimen is passed into another bottle and still a third after being up and around for an hour without eating or drinking Fishberg writes

> The specific gravity of each of the three specimens is then taken If kidney function is unimpaired the specific gravity of at least one of the specimens will exceed 1 022 often going as high as 1 032 In very severe impairment of renal function the maximum specific gravity is but 1 010 and in intermediary cases figures between these extremes are obtained In every case exhibiting low specific gravity it is important to observe if edema is being evacuated for this may simulate inability to concentrate The third specimen passed while the patient is up and about occasionally helps in the detection of orthostatic albuminuria

Albumin Albuminuria is an almost constant finding in congestive heart failure the greater the congestion the more the albuminuria In the absence of any trace of edema its presence is far more significant of renal disease unless it is the slight inconstant so called orthostatic albuminuria or an accompaniment of infection In the case of subacute bacterial (Streptococcus viridans) endocarditis there is often important renal bleeding and damage albuminuria is therefore a frequent finding in this disease

Sugar Glycosuria may be transient slight and unimportant it may be of alimentary origin or the result of some accident like cerebral hemorrhage but usually it indicates diabetes mellitus mild or severe and then demands particularly conservative treatment in cardiovascular patients (see Chapter 23)

Urinary sediment Generally when there is congestive albuminuria red and white blood corpuscles and granular and cellular casts are found in the sediment of the urine With chronic nephritis hyaline casts are more frequent than in congestive heart failure With subacute bacterial endocarditis even though

there be no albuminuria red blood corpuscles are usually found in the sediment Gross blood in the urine is always important but is more likely to be due to local infection stone or malignancy than to heart disease Renal infarction secondary to emboli from a diseased heart in subacute bacterial endocarditis myocardial infarction with intracardiac thrombosis or mitral stenosis with atrial fibrillation is however an occasional cause of gross hematuria

Renal function tests The various tests of renal function simple or more elaborate may be applied in the presence of cardiovascular disease but their interpretation must be guarded The disturbance of renal function may be dependent on either renal disease or secondary congestion from heart failure The degree of renal impairment as indicated by most of the functional tests is dependent rather on the degree of involvement of the kidneys whether primary or secondary than on the type of involvement The combination of both primary and secondary involvement naturally results in the gravest disturbances of function One must wait until congestive failure subsides before making many deductions from renal function tests The most practical and useful tests are the urine concentration test such as that described above under Specific Gravity and the red (phenolsulfonphthalein) test in current use everywhere emphasizing however more the rapidity than the amount of the excretion It is more important to know what percentage of the dye is excreted in the first 15 minutes (normally 25 per cent or more) than in the total time of two hours (60 per cent or more)

CARDIAC OUTPUT MINUTE VOLUME OF BLOOD FLOW AND CIRCULATION RATE STUDIES PLETHYSMOGRAPHY

Cardiac output The cardiac output the minute volume of the blood flow and the speed of the circulation have been subjects for physiologic investigation for years chiefly in animals in the experimental laboratory During the last decade the application of such study to clinical medicine has been successfully begun

Long ago it was shown experimentally that the amount of blood pumped out by either ventricle in the course of a minute called the *minute volume of blood flow* could be determined readily by a formula (Fick 1870) based on the amount of oxygen taken up by the lungs in a minute s time and the amount utilized by the tissues This formula is as follows

$$\text{Minute volume of blood flow (in cubic centimeters)} = \frac{100 \times \text{cubic centimeters oxygen consumed in lungs per minute}}{\text{Difference in volumes per cent between oxygen content of arterial blood and that of venous blood}}$$

The application of this formula to man was for years fraught with difficulties though the discovery that analysis of the alveolar air permitted a close ap-

proximation to that of the blood gases of the right and left sides of the heart proved very helpful so that the minute volume of man could be ascertained and through that the stroke volume or output of each ventricle per beat (by dividing the minute volume by the pulse rate) Another method for determining blood flow was also used dependent on the absorption of certain gases from the lungs in a certain unit of time for example nitrous oxide acetylene and ethyl iodide acetylene proved to be the most suitable gas for this study (Grollman 1932) ethyl iodide giving figures 33 per cent too small

The introduction in recent years of cardiac catheterization has permitted a more accurate determination of the minute volume of blood flow by the use of the Fick formula since the oxygen content of the mixed venous blood in the right heart chambers can be readily measured and compared with the oxygen content of arterial blood This volume divided by the pulse rate gives the cardiac output per beat

Hamilton and his associates (1947 and 1948) have compared the Fick dye injection and pressure pulse curves in dog and man in relation to the cardiac stroke volume and have found a fair correlation between the dye injection and Fick findings and a close approximation between dye injection and pulse pressure contour

The application of heart volume changes between systole and diastole as determined roentgenologically has also been suggested recently (Hubacher and Nyffeler 1946) the difference in volume representing directly the stroke volume The difficulties inherent in measuring the heart volume by x ray however present a problem here that needs further development (see Chapter 7)

An ingenious but crude method of determining the output of the heart per beat and per minute was introduced by the use of the *ballistocardiograph* (Starr and Schroeder 1940 Cournand Ranges and Riley 1942) This instrument which consists of a delicately balanced table (on which the subject reclines) records the recoil of the body when the blood is ejected into the aorta and pulmonary artery from the ventricles Attempts have been made to correlate the graphic record which results called the ballistocardiogram (see Chapter 8) with the output of the heart as determined by the more direct methods noted above and can apparently with considerable corrections be used as a rough though inadequate gauge of the cardiac output the latest studies have indicated that the ballistocardiographic index was about one third too low Thus ballistocardiography is best used as a method of study per se and not to determine the cardiac output (see Chapter 8 and Figure 38 page 172)

The minute output at rest normally ranges from 3 500 to 9 000 cc (6 to 12 cc per 100 gm of body weight) being increased by exercise to as high as 25 liters or more in some cases It may like the stroke volume be reduced by various factors but usually to a less degree since an increase of pulse rate tends to compensate for a decreased output per beat The erect posture has been found usually to cause a decrease (even as much as 30 per cent or more

but usually less) of the minute volume calculated for the recumbent position Various other factors influence blood flow in a definite but sometimes indeterminable degree these are the stroke volume of the heart the lung capacity the absorption power of the lungs and the capillary diffusion areas of muscles Physical training makes these factors more favorable and so enables the circulation to be carried on more economically with less strain on heart and arteries as indicated by less elevation of pulse rate and blood pressure on exertion in the athlete than in the nonathlete Heart failure is usually attended by a decreased output but this is very variable and in some cases, as in thyrotoxicosis the output may still be elevated

It has been found that the normal output per beat or stroke volume varies in the average adult from 50 to 100 cc at rest but that in athletes it may be much higher, even 150 cc or more This is increased by exercise less in the nonathlete than in the athlete it may be more than doubled rising for example from 60 to 130 cc or from 70 to 150 cc on vigorous exercise With heart failure or extreme tachycardia it may be reduced in a case of paroxysmal tachycardia for example it has been reported to have dropped from 77 to 13 cc (Barcroft Bock and Roughton 1921)

Circulation rate In the past the volume of blood flow has been studied more than the rate but ingenious methods for determining the *rate of blood flow* through important parts of the circulatory system have been devised A pioneer method consisted of the injection of an active deposit of radium into the vein of one arm and the determination by means of a detector of the moment of its arrival in the heart and in the artery of the other arm (Blumgart and Yens 1927 Blumgart and Weiss 1927) The speed of flow from *arm vein to heart and through heart and lungs to arm artery* was thereby roughly determined Normally this arm to arm circulation time was found to vary from 14 to 24 seconds (average 18 seconds) a somewhat longer time than has been the finding in the case of more recently introduced substances injected this time increased with the pulse rate but not with blood pressure variations and was not affected by valvular disease The circulation rate was found to be decreased in congestive heart failure according to the degree of failure and also in atrial fibrillation without failure Arteriosclerosis and pulmonary emphysema did not cause a delay The arm vein to heart rate of travel of the radium injected blood showed a wide range of 2 to 14 seconds with an average of 7 seconds in normal individuals

The recent introduction of the employment of safe radioactive isotopes has revived this earliest method of determining the circulatory rate Hubbard et al (1942) tested the velocity of blood flow in infants and young children using radioactive sodium, Prinzmetal et al (1949) found the arm to right heart time to average 2 seconds normally in the adult with an dditional 5 or 6 seconds to the left heart

Since the earlier days of the clinical application of the study of the rate of the circulation a decade or more ago numerous new methods consisting mostly of substances for injection into an arm vein have been introduced

These have included injections of a dye (brilliant vital red for example) fluorescein histamine (which flushes the face) sodium cyanide (causing a sharp increase in respiration) lobeline (causing a deep inspiration followed by a cough) Decholin (sodium dehydrocholate) (giving a bitter taste) glucose or saccharine (detected in the systemic circulation of the tongue by a characteristic taste) aminophyllin amyl nitrite (lung to face time as determined by a hot sensation) and calcium gluconate and magnesium sulfate (both causing a sensation of heat in pharynx and tongue) to test the rate of the blood flow from the venous side of the systemic circulation through the right heart lungs and left heart into the arterial side of the systemic circulation There is a wide range of sharpness of end point and of practicability among these various substances Hitzig (1947) and Blumgart and Altschule (personal communication) have preferred the use of Decholin with end point at 10 to 16 seconds which however has in rare cases caused allergic like reactions (Norman 1947) Baer (1940) found calcium gluconate the most desirable in 133 normal persons he found the arm vein to tongue time to range from 8 to 16 5 seconds averaging 12 3 seconds He injected 4 cc of 20 per cent calcium gluconate rapidly and then again in 2 or 3 minutes Papaverine HCl has also been suggested for determining the circulatory rate (Elek and Solarz 1942) 40 mg (1 25 cc) being the dose recommended an average of 20 8 seconds (15 4 to 27 0) has been reported between the time of injection and that of the end point a sudden deep inspiration In experimental animals acetylcholine has been tried with end point measured by direct inhibitory effect on sinoatrial node (Wilburne et al 1947)

To test the arm to lung time that is the integrity of the venous side of the systemic circulation and the right heart the injection of ether (Hitzig 1935) has been most practicable (using 5 minims of ether and 5 minims of normal saline) with end point detected by the subject s consciousness (or even the observer s note) of the presence of ether on the breath Baer (1940) found the ether arm to lung time in 169 normal individuals to vary from 3 to 9 seconds averaging 5 8 seconds Paraldehyde has also been introduced to test the arm to lung time (Caudel 1938)—the end point is shown by a cough in 100 adults with normal hearts the range was from 3 to 9 5 seconds averaging 6 seconds

Finally the inhalation of CO has been suggested to test the lung to brain time that is the integrity of the pulmonary circulation and left heart (Gubner Schnur and Crawford 1939) acting as a stimulant to the respiratory center its normal range has been found to be 5 to 10 seconds

Several investigators (Germandt and Nylin 1946 Meneely and Chestnut 1947 Nathanson and Elek 1947) have pointed out the delay in circulation rate that may occur as the result of dilatation of the heart alone even without congestive failure there remaining a certain amount of residual blood in the heart chambers immediately after their contraction

The tests of circulatory rate ordinarily employed are the ether time (normal average about 6 seconds) to determine the state of the right ventricle and

Decholin saccharine, or cyanide time (normal average 12 to 15 seconds) to test the total heart efficiency the subtraction of the former from the latter gives an estimate of the strength or failure of the left ventricle The tests are useful in a few cases in which there is some doubt especially in distinguishing in obscure cases between bronchial and cardiac asthma and in following given patients by serial tests but they are not routinely necessary

Plethysmography Plethysmography that is the measurement of volume changes of extremity or organ has been carried out chiefly in experimental animals but for certain purposes has been also applied to man It has been used to measure blood pressure to obtain fairly accurate records of the arterial pulse wave and especially to measure the volume of blood flow in a special part of the body It has little application to routine cardiovascular examination but in obscure or difficult cases of peripheral vascular disease it may yield information of value Of late a study of the electrical impedance of an *extremity has indicated its possible use in the application of an electrically* recording plethysmograph to investigations of the peripheral circulation (Nyboer 1950)

CALCULATION OF THE WORK OF THE HEART AND OF THE PULSE

Various attempts have been made to estimate the actual work of the heart and of the pulse some of these have proved of interest but they have not been of any practical value in cardiovascular examination We can for example express by a very rough formula the work of the left ventricle when we know the volume output per beat the heart rate and the mean arterial blood pressure If the left ventricle expels 100 cc of blood per beat at a rate of 60 beats per minute at a mean arterial pressure of 100 mm of mercury (about 1 300 mm of blood) it lifts 6 liters (6 000 cc) of blood to a height of 10 cm of mercury (or about 130 cm of its own weight) per minute which equals 780 000 gm-cm (or 7 8 kg meters) per minute The blood vessels maintain this volume at a somewhat lower level through diastole in addition to withstanding the systolic shock of the heart This rough calculation expresses in an interesting way the enormous constant activity of the heart It may further be applied to certain pathologic states for example if the mean arterial blood pressure is 150 mm of mercury and the heart rate 60 per minute and the output per beat 100 cc the work of the heart is 50 per cent greater than in the previous example given or 11 7 kg meters per minute Such a great increase in work if constant can explain the hypertrophy of the left ventricle found in hypertension

It has been calculated (Remington and Hamilton 1947) that the cardiac work performed in maintaining pressure is underestimated up to 12 per cent by multiplying the total ejection by the mean pressure during systole and that the work done by the heart in raising the pressure of the blood is 10 to 40 per cent more than that done at the periphery in forcing blood through the peripheral resistance energy to this amount being lost as the aortic wave is damped

More accurate formulas to include still other variables like velocity the effect of gravity and time intervals have been devised such as the following (Evans 1918)

Work of heart $= 7\frac{Q \times R}{6} + \frac{W\ (V \times C)}{G \times E}$ where Q equals the quantity of blood ejected R equals the mean arterial resistance in meters of blood W equals the weight of the volume ejected V equals the mean velocity C equals the duration of the cardiac cycle G equals the acceleration due to gravity and E equals the period of systolic ejection The complication and incompleteness of such a formula however renders it impracticable except for experimental animals moreover it represents not the work of the whole heart but of the left ventricle alone The need of determining the output of the heart per beat by special methods the difficulty of ascertaining the mean arterial pressure the need of cardiac catheterization to estimate accurately the work of the right ventricle because for such calculation the pulmonary blood pressure must be measured in man and the apparent relative unimportance of the knowledge of the exact amount of work done by the heart have caused the general and probably justifiable neglect of such calculations as these in cardiovascular examination It is possible however that more attention paid to the actual work of the heart would be helpful at least in causing one to realize the great variability that exists not only in disease but also in health

Calculation of the work of the pulse as determined for example by sphygmobolometry (Sahli) or energometry (Christen) or otherwise has proved very complicated and of no practical value

FUNCTIONAL TESTS OF THE HEART AND OF THE CIRCULATION

Strength and endurance tests Both simple and complicated measures of strength and endurance have been proposed to gauge the health of the heart muscles and of the circulation as a whole These measures do demonstrate efficiency of the heart along with that of the muscles and nerves but it is frequently difficult to conclude to what degree abnormal limitation of strength and endurance is due to exhaustion how much to nervous fatigue and how much to myocardial weakness Dyspnea and angina pectoris are the two chief cardiac symptoms of overtaxation of the myocardium and when these symptoms are clearly singly and in a preponderant degree produced by tests of physical activity we may obtain valuable information about the heart When a sense of exhaustion in local muscles or generally throughout the body or when palpitation dizziness and faintness appear with or without dyspnea or heartache (not angina pectoris) other factors then enter in which prevent carrying the exertion far enough clearly to test the heart s rength this is the usual situation because of the general lack of physical training or because of the ready nervous fatigability in most individuals tested Hence these tests of strength and endurance generally amount to tests of training and of the nervous

state that is of physical fitness rather than of cardiac condition Neurocirculatory asthenia (or effort syndrome or soldier s heart) and muscular flabbiness are more easily and often exposed by exercise tests than is heart disease Nevertheless tests of strength and endurance may be applied with some success in estimating myocardial efficiency if sound judgment be shown in the interpretation of the findings

The simpler the test the better because a simple test is less likely to strain unaccustomed muscles less likely to exhaust prematurely a person not in good physical training and more convenient and practical to execute In fact such simple exertion as enters into the routine daily life of the patient is best of all. Questioning alone may suffice as to the production of dyspnea or of angina pectoris by climbing a flight or two of stairs at an ordinary rate of speed climbing a hill of moderate grade at moderate pace walking fairly rapidly on the level or lifting and carrying a handbag suitcase or heavy overcoat But if there is doubt or a need for exact data actual tests of these activities under the observation of the examiner should be executed Climbing a flight or two of stairs or if that seems too much pacing rapidly up and down the room or corridor or mounting and descending repeatedly an especially constructed two-step footstool are perhaps the best of the simple exercise tests A word of warning should however be added here namely that exercise testing in the case of serious coronary insufficiency can prove fatal

Under some circumstances as for example in examinations for military service athletic sport or other such activities more vigorous or special tests are suitable such as weight lifting hopping running and stepping repeatedly from floor to chair seat and back again Since however in routine civilian practice one deals often with older men and women or untrained persons with weak or undeveloped muscles these exercises are not usually applicable A trained athlete physically fit but with well marked aortic regurgitation may carry out vigorous exercise tests without any trouble while an untrained soft muscled man of the same age height and weight with a normal heart may be unable to complete relatively light exercise tests without much fatigue dyspnea and palpitation

The reaction of pulse rate and of blood pressure to exercise has been the subject of considerable study and discussion and has at times been thought to be a suitable test of circulatory efficiency, but the same remarks apply to this as to the production of symptoms Too marked a rise of pulse or blood pressure and too long a duration of this rise after rest begins go with poor physical condition as often as with cardiac weakness alone Normally after a short spell of exercise of moderate degree (like climbing rapidly two average flights of stairs or lifting during a time interval of one minute two five-pound dumbbells twenty times from the floor first to a standing position and then to an extended position of the arms above the head) the pulse rate and blood pressure in a well trained young or middle aged adult should return to normal from elevated levels within two minutes after lying down The more vigorous the exercise the more slowly do blood pressure and pulse rate return

to resting figures even in the normal subject The delayed rise of pressure is also of little or no significance normally there is a slight immediate fall when exercise begins before the rise develops

Over a period of many years various functional tests have been introduced under the names of their respective proposers but thereafter as a rule speedily forgotten Cabot and Bruce for example in 1907 described a group of such tests and imposed a modification of their own There has however been in routine use for quite some years especially in military circles a certain test for general physical and circulatory efficiency which despite its obvious im perfections has continued to be commonly employed This is the Schneider Index (1920) It is carried out as follows

1 The patient reclines for five minutes (a) The heart rate is then counted for twenty seconds When two consecutive twenty second counts are the same this is multiplied by 3 and recorded The score is noted according to Part A Table 1 (b) The systolic blood pressure is next taken by auscultation two or three readings are made as a check

2 (a) The patient stands at ease for one or two minutes to allow the pulse to assume a uniform rate When two consecutive twenty second counts are the same this is multiplied by 3 and recorded The score is obtained by the use of Part C Table 1 The difference between the standing and reclining pulse rate is scored then by use of Part B Table 1 (b) The standing systolic pressure is next taken The difference between this and the reclining systolic pressure is then scored by Part F Table 1

"3 The patient next steps on a chair about 18 inches high, five times in fifteen seconds timed by a watch To make this test uniform he stands with one foot on the chair at the count one this foot remains on the chair and is not brought to the floor again until after the count five At each count he brings the other foot on the chair and at the count down replaces it on the floor This should be timed accurately so that at the fifteen second mark both feet are on the floor (a) Imme diately while he stands at ease the pulse rate is counted for fifteen seconds this is multiplied by 4 and recorded (b) Counting is continued in fifteen second intervals for two minutes record being made of the counts at 60 90 and 120 seconds

The data from (a) will be scored by Part D Table 1 taking the difference between this exercise pulse rate and the standing rate The data in (b) are scored according to Part E Table 1

The total score is then added up in Parts A B C D E and F of Table 1 (see next page) The maximum possible is plus 18 and the minimum is minus 11 A score above plus 9 is considered normal a score of 9 or less fails to pass and is reason for a search as to the cause

A newer test of physical fitness for strenuous exertion superior in its appli cation to athletes and simpler in its execution than the Schneider Index was developed at the Harvard Fatigue Laboratory and is called the Fatigue Lab- oratory Index (Johnson Brouha and Darling 1942) It is carried out as follows The subject works at a standard hard exercise until he is exhausted

or if not exhausted for five minutes The pulse is counted in recovery from 1 to 1½ from 2 to 2½, and from 4 to 4½ minutes The score is calculated from the formula

$$\text{Index of fitness for hard work} = \frac{\text{Duration of exhausting work in seconds} \times 100}{2 \times \text{sum of pulses from } 1\text{–}1\tfrac{1}{2},\ 2\text{–}2\tfrac{1}{2} \text{ and } 4\text{–}4\tfrac{1}{2} \text{ minutes after the end of work}}$$

The larger the score the better the subject 100 being a very good score Any form of exercise can be used provided it puts sufficient stress on the circulatory system by involving large muscle groups provided not more than two

Table 1

POINTS FOR GRADING CARDIOVASCULAR CHANGES IN SCHNEIDER S TEST OF PHYSICAL FATIGUE AND EFFICIENCY

SCHNEIDER INDEX

A Rei ting pulse rate		*B Pulse rate increase on standine (points)*				
Rate	*Points*	*0–10 Beats*	*11–18*	*19–26*	*27–34*	*35–4*
50– 60	3	3	3	2	1	0
61– 70	3	3	[illegible]	1	0	1
71– 80	2	3	2	0	−1	[illegible]
81– 90	1	[illegible]	1	−1	−2	−3
91–100	0	1	0	−2	−3	3
101–110	−1	0	−1	−3	−3	3

C Standing pulse rate		*D Pulse rate increase immediately after exercise*				
Rate	*Points*	*0–10 Beats*	*11–20*	*21–30*	*31–40*	*40 50*
60– 70	3	3	3	2	1	0
71– 80	3	3	2	1	0	0
81– 90	2	3	2	1	0	1
91–100	1	2	1	0	−1	−
101–110	1	1	0	−1	−2	−3
111–120	0	1	−1	−2	−3	3
121–130	0	0	−2	−3	−3	−3
131–140	−1	0	−3	−3	−3	−3

E Return of pulse rate to (standing) normal after exercise

Second	*Points*
0– 30	3
31– 60	2
61– 90	1
91–1..0	0
After 120 two to ten beats above normal	−1
After 1 0 eleven to thirty beats above normal	[illegible]

F Systolic pressure standing compared with recling

Change in mm	*Points*
Rise of 8 or more	3
Rise of 2–7	2
No rise	1
Fall of 2–5	0
Fall of 6 or more	−1

thirds of the subjects can maintain it for five minutes and provided it does not demand some unusual skill for its successful performance The only equipment needed is a stopwatch and a means of administering a known amount of exercise at a constant rate Detailed instructions are given for using the test when a treadmill is available

Respiratory tests Most of the respiratory tests that have been employed to study circulatory efficiency are restricted in the same way in their clinical application as are the strength tests described above But here a further complication exists Diseases of the lungs pleurae or respiratory muscles can cause striking reductions in scoring just as can general weakness neurocirculatory asthenia and certain cardiac lesions

There are various respiratory tests the most practicable two being that of the vital capacity and that measuring the length of time that the breath can be held More complicated tests which measure symptom and pulse and blood pressure reactions to certain respiratory efforts such as maintaining an elevated air pressure in a closed system for a certain length of time or re breathing air in a closed chamber are open to the same objections as those already expressed concerning exercise tests they are tests of physical fitness more than of heart disease or failure also they are affected at times by the additional factor of possible pulmonary disease Although they may reveal myocardial insufficiency the degree of this must be very carefully interpreted and judged

Vital capacity The vital capacity of the lungs is the measurement by spirometer of the amount of air in liters that can be expelled by a complete forceful expiration after the fullest possible inspiration This test was first studied in considerable detail over a century ago (Hutchinson 1846) Normally the vital capacity varies with the size of the individual which is best calculated from the surface area the surface area can in turn be estimated roughly but accurately enough from the height and weight The normal ratio averages 2 5 liters of vital capacity per square meter of body surface A chart has been devised for the determination of surface area (Figure 28B page 143) and tables of average normal vital capacity for male and female American subjects have been constructed The vital capacity ranges normally from 3 to 4 liters for adult females and from 4 to 5 liters for adult males It varies somewhat with practice increasing as a rule on repeated tests until the subject becomes expert It varies also with physical fitness An athlete has a higher vital capacity than a nonathlete by as much as 25 per cent or more Furthermore the vital capacity is between 5 and 10 per cent higher in the erect than in the recumbent position In severely exhausted states and in marked neurocirculatory asthenia it may be much reduced even to 2 liters or less in an adult who is otherwise healthy with normal heart and lungs If inexperience exhaustion and lack of physical training are excluded as factors vital capacity reduction means infection thyrotoxicosis or pulmonary pleural mediastinal or cardiac disease

Vital capacity was originally studied to ascertain the degree of pulmonary

disease such as phthisis in which it is usually reduced Of primary cardiac conditions there are chiefly two that give rise to reductions of vital capacity mitral stenosis and congestive heart failure Pulmonary emphysema no matter what may produce it fundamentally is also an occasional cause of reduction of the vital capacity The greater the degree of any of these conditions cardiac or otherwise the lower is the vital capacity especially in the case of heart failure when there may be a reduction to below a liter such a high degree of reduction does not happen with uncomplicated mitral stenosis It has been reported that if there is pulmonary edema breathing dry air may increase the vital capacity as much as 10 per cent or more (Leas 1927)

The chief value of the vital capacity measurement in the study of a cardiac patient is in following the course of congestive failure A chart showing the vital capacity at intervals daily or every few days is of interest and sometimes of value in such cases but the test is a crude one and lags behind other evidence of change in the patient as often as it precedes it It may be concluded that the estimation of vital capacity in cardiovascular examination is not important as a routine measure except perhaps in pregnancy with heart disease when exertion is by order much restricted and reduction of the vital capacity may be the first indication of impending heart failure It is not delicate enough to demonstrate very slight grades of cardiac insufficiency and it does not give evidence of organic heart disease in the absence of failure except in the case of mitral stenosis which acts to decrease the alveolar air by causing engorgement of the lung vessels

Breath holding test A very simple respiratory test probably as useful as any other and because of its ease of execution the most practicable is the measurement of the length of time the breath can be held after a full inspiration All the qualifications with respect to the circulation made above concerning exercise and respiratory tests apply here also The breath holding test has one defect which applies only to certain cases and that is the possibility of malingering noted sometimes in soldiers during World War I it is possible however with experience to detect malingering Practice is sometimes important, as in the case of the vital capacity test A normal person in good physical and mental condition should be able to hold the breath for more than half a minute usually about three quarters of a minute and occasionally for over a full minute Extensive and expert training in underwater swimming and diving may enable an individual to hold his breath as long as two or three minutes or even a bit longer If the breath cannot be held as long as a half minute the test shows abnormality consisting of pulmonary or pleural disease congestive heart failure or lesser grade of cardiac insufficiency mitral stenosis general weakness or neurocirculatory asthenia

Anoxemia test The so-called anoxemia test was clinically introduced by Levy and his associates in 1939 to determine the functional capacity of the coronary circulation especially in persons suspected of having coronary heart disease but without clear-cut angina pectoris or electrocardiographic abnormalities The test is carried out as follows The subject breathes a mixture of

10 per cent oxygen and 90 per cent nitrogen for twenty minutes unless cardiac pain is experienced before the end of that time Electrocardiograms (preferably the precordial leads first) are taken routinely just before the test is started and at intervals of five minutes thereafter If the patient complains of dis comfort a record is quickly taken the low oxygen mixture is shut off and 100 per cent oxygen administered for one minute

Two hundred and ninety three of these tests were carried out by Dr Levy and his associates 136 were done on persons apparently free of cardiac diseases and 157 were done on patients with coronary sclerosis Pain was not induced in any of the normal cases 74 or 47 per cent of the coronary cases complained of pain in 54 of which the pain came on during the first 10 minutes Positive electrocardiographic tests were observed in 77 or 49 per cent Positivity of the test was considered to be a total *RS ST* deviation greater than 2 5 mm Deviation was most marked in Lead 1 and in the precordial leads

The test has been found useful by Levy and his associates in doubtful cases but has not yet been widely adopted Some question of its safety has been raised and of the interpretation of slight electrocardiographic variations which might be within the range of normal (Burnett et al 1942) but in the hands of Levy and his associates (1941 and 1942) and of others since the test has apparently proved both useful and safe Careful clinical appraisal however makes rarely necessary either this anoxemia test or exercise tests though there are always a few individuals in whom the diagnosis may be difficult and for whom such tests are helpful if positive negative tests do not however rule out serious coronary heart disease with certainty

Tests of the peripheral circulation Numerous tests of the efficiency of the peripheral circulation have been introduced from time to time A decade ago a review (Montgomery Naide and Freeman 1941) summarized their diag nostic importance The tests have been divided into four groups (A) those which are a part of the physical examination and include observation of local tissue nutrition color and temperature of skin palpation of pulse and estima tion of blood pressure in different limbs at various levels rate of blanching on elevation and of flushing and filling of veins on dependency and the repro duction of spasm by immersion of the extremity in cold water (B) tests of capacity of blood flow (vascular function tests) in skin as shown by vaso-dilatation by reflex heat artificial fever anesthesia (local general spinal and paravertebral) intradermal histamine and saline injections and reactive hyperemia (C) tests of capacity for blood flow (vascular function tests) in muscle by walking certain distances and by ergographic measurements of muscle fatigue and (D) test of past damage to arteries by oscillometry and roentgen ray studies especially by Diodrast injection of arteries or veins An additional method of study (E) has been more recently introduced consisting of the injection of radioactive isotopes especially sodium and following its course through any local circulatory area by Geiger counter (Elkin et al 1948) As in the case of judgment about the heart by tests so here too much

experience and common sense are needed for proper appraisal in many of the cases

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PART II

THE SIGNIFICANCE, PREVALENCE, CAUSES, AND TYPES OF HEART DISEASE

CHAPTER 11

THE SOCIAL AND ECONOMIC ASPECTS OF HEART DISEASE

Introduction The significance of heart disease is far reaching penetrating and affecting the health and happiness work and lives of all peoples on earth and from the cradle to the grave Belatedly the medical profession has at long last taken cognizance of this fact and has begun to enlist the support of patients social groups universities foundations and finally of local and national governmental resources in the growing struggle to elucidate the causes of heart disease and thereby to clear the way for their control

Heart disease or rather cardiovascular disease has become the chief public health problem of our day Ranking as the leading cause of death it has been widely but crudely publicized unwarranted fear of heart disease has swept the country in fact all the world Although it is true that the most recent and most accurate statistics do show a high incidence of cardiovascular deaths three very important considerations counterbalance in large part the serious ness of such a state of affairs In the first place cardiovascular disease or in deed heart disease itself is not just one disease but actually a multitude of different diseases most of which are quite unrelated except as they all involve the heart or blood vessels thus heart disease is very different from tuberculosis or typhoid fever or even cancer Secondly the increase in heart disease is in the older age groups there having been *actually a decrease in recent years* in heart disease mortality below the age of twenty five in the United States (Hedley 1939) An old person must die eventually of some disease process and a circulatory death is as good to suffer as any indeed probably better than many others Finally many grades of heart disease of various types are contrary to old time tradition mild and relatively unimportant compatible with considerable longevity and full activity

However despite these favorable points about heart disease it still leads other diseases as a cause of death from the age of five years to that of twenty it cripples many thousands of young people as the result of congenital defects and of rheumatic involvement of heart muscle and valves and it strikes down many leaders in professional business and political life in middle age at the

height of their careers of usefulness Thus there are many aspects of heart disease that concern society and national economy, in the home in the school in industry in the community and in the nation The present chapter has been newly added to this book in order briefly to discuss these special problems

Heart disease as it affects the home Heart disease presents many problems for the home which include the effects both of the chronicity of the condition and of the acute attacks that are so likely to punctuate its course Thus in children there are periods of rheumatic fever often very prolonged which require much patience of the family whether the youngster is in bed at home or away in a hospital or convalescent establishment Since many times in the absence of specific therapy these attacks last for months both child and parents become much depressed and need cheerful medical and nursing care It has been here that expert social service pioneering and recreational therapy when the state of health permits have played in late years an important role At the Massachusetts General Hospital Miss Edith Terry and Miss Lorena Love have established under the aegis of the Committee for the Home Care of Children with Heart Disease the In Bed Club with its badge and jacket and magazine home visiting schoolteachers and occupational therapy have added their share of aid for these children even before they graduate from bed to rejoin their comrades in the usual life of the community Not only are these patients followed in this encouraging manner while acutely and subacutely ill but they and their parents are seen at intervals thereafter to help them from acquiring the attitude so common in the past of resignation to lives of invalidism and fear Often the families need more instruction and building up of morale than do the children themselves And when much schooling is lost it has been found possible by easygoing and well controlled summer courses to promote the child to the class ahead along with his mates In Boston a good additional resource in the care of these children when subacutely ill has been the special foster homes of the Children s Mission when home care proved difficult and hospital attendance impossible or too prolonged

For the mother ill with heart disease acutely in childbearing age or older or chronically disabled the choice of an able and understanding housekeeper is not infrequently more important even than nursing care to relieve both mother and family of undue worry such a person can herself help with the actual nursing too unless the illness is very severe Another problem concerns the need in some cases of limitation of the size of the family and hence of some method or other of birth control expert advice is here often necessary since the risk of childbirth or even of a needed termination of pregnancy should not be countenanced

For the father ill with heart disease the threat of disability and death leaving the family not infrequently inadequately supported requires much careful planning with expert and friendly advice of doctor and business and professional associates It often in fact usually is not necessary for the man with heart disease to retire from his life work except perhaps for a few weeks or

months even after an acute coronary thrombosis. Years ago it was common practice to advise retirement in such a case but fortunately we have learned better in the last twenty five years. Moreover it is wise for a man young or middle aged immersed in his business or professional life to cultivate an avocation or hobby or two not too strenuous to which he may turn with pleasure if in later life he is prevented by illness cardiac or of other sort from continuing his business or professional life or indeed when he retires simply because of age.

Finally there are the elders of the family grandparents and great grand parents who may have heart trouble the commonest ailment of the aged. They may be a great burden for their juniors not only medically but socially and financially as well especially if they perforce reside with them. Much better planning in the future will be needed than in the past to help solve this difficult problem especially since there will be constantly more and more old people in the world. They themselves must plan better for their future when they are young their families must acquire a better attitude toward their elders with the respect for age that has been the Chinese tradition and finally the medical profession and the community itself must devote more time and interest to this problem of the care of old age which has been vari ously called gerontology and geriatrics a special field that will one day rank in interest and importance with pediatrics.

Heart disease as it affects the school The youngest school children five and six years old may have heart disease either congenital or the beginning of rheumatic. In fact these troubles may delay their entrance into school life by a year or more either because of the severity of the symptoms of the morbus caeruleus or because of active rheumatism which may be severe and prolonged at this early age and require months of bed rest. Except for these two conditions however most children with heart disease at any age can safely and profitably attend school and need not in fact should not be separated off in special categories or classes except for rare individuals who are unusually crippled by early and marked valvular deformity cardiac arrhythmias or congenital defects of noncyanotic type. It has not been found necessary to establish as at one time was planned special cardiac classes in the public schools. Happily however in many communities home visiting is carried out by public and private schoolteachers when the children are well enough to receive them thus keeping up both instruction and morale. And when the children do get back to school there is often a sensible arrangement whereby they may be watched and guided without making them overanxious resentful or set apart to do this there can wisely be a cooperative plan of schoolteachers parents and family doctor.

The instruction itself in the upper classes in the teens can be skillfully directed toward an interest in sedentary occupations later in life if there is much heart trouble but often there is so little wrong (as for example slight mitral valve deformity or a small ventricular septal defect) that there need be no restrictions whatsoever present or future. The same principles apply to

athletic sports and gymnastic exercises Infrequently it is necessary to curtail them but often it is wise to direct a child to baseball in preference to basket ball hockey or football and to short races and jumping in preference to marathon runs crew races, distance swims and heavy skiing

Most important of all in these various considerations is the individual himself No two patients are exactly alike and so it is vital to decide about every case on its own merits

Heart disease as it affects industry, business, and professional life In the past there has been much unnecessary fear of heart disease in its relationship to industry but happily a saner attitude is now developing as the result of informing the public at large of the accumulating experience of the medical profession During the last generation it has become quite evident in the first place, that the majority of persons with heart disease live a good many years after its onset in the second place that the great majority of such long survivors can live useful and contented lives and *finally that they are with* uncommon exceptions benefited rather than harmed by work to which they are accustomed for which they have been trained and which they enjoy Far too many cardiac invalids have resulted from the oversolicitous attitude of family friends or even physicians themselves and from the apprehension of industries businesses and professional associates and clients A recent survey of opinions of experts of the American Heart Association Committee of the Effect of Strain and Trauma on the Heart and Great Vessels has con firmed the experience of the author in this respect namely that the routin activity of persons in industry business and the professions if carried on in a sensible manner neither initiates heart disease nor makes it worse if it is already present unless it is very severe or going through an active stage as in the case of acute rheumatic carditis of acute or subacute coronary insuffi ciency or of myocardial insufficiency Under the conditions of such compli cations omission of work and rest at home or in hospital are of course in dicated but often only temporarily for after these conditions have cleared up many persons can safely resume work to advantage to both morale and physical health to say nothing of their economic status in the support of themselves and of their families

One must of course separate off from the routine strains of industry business and the professions accidents and trauma physical or mental which can occur just as often at home or at play or in the crowded traffic of the present day (see Chapter 23) As a matter of fact acute coronary throm bosis and deaths from angina pectoris and cerebral vascular accidents are much more likely to occur away from work than on the job and often even in bed There should be a clearer understanding by industry and more wide spread satisfactory insurance laws to meet the problem of the person with heart disease than have existed in the past One of the pioneers (Dr Irving Clark) in this regard who has had experience over many years in the em ployment of cardiacs in industry has emphasized the value and safety of so doing slowly this word is getting about Of course there must be safeguards

such as a careful appraisal of the individual at the beginning an examination annually or oftener if the need arises and proper treatment when complications come as they may whether the person is working or not Industry should not be blamed for such complications any more than some trivial accident which may have brought to light heart disease which has existed for years On occasion some unusual strain or trauma may expedite a complication and if so a justifiable and satisfactory attempt can be made to apportion the responsibility of such an exciting factor in the overall picture for example in a patient with a moderate or considerable degree of mitral stenosis some special strain may set off atrial fibrillation which might not have come on otherwise for some weeks or months or even a year or two but such strain should not be considered as 100 per cent responsible for the temporary disability that results it may not rate more than 10 per cent

These remarks apply to every kind of heart disease even the morbus caeruleus but of course youngsters with severe congenital or rheumatic heart disease should be trained in their youth for sedentary occupations and oldsters may need to reduce their time at work or sit instead of stand or shift to another job With regard to changing occupations one should add that a somewhat active job for which a person is trained at which he or she is skillful and which is well liked may afford actually far less strain than a new job which seems easier physically but which may prove both difficult and boring for the person concerned Thus one must individualize advice for every case lists of occupations for cardiacs may be somewhat useful bu they are only rough guides at best

We should not deprive our cardiac patients of education or some sort of occupation just because they seem hopelessly handicapped A good lesson in that respect was taught by a patient of mine with a high degree of the tetralogy of Fallot who because of much cyanosis and delicate health in early childhood received no schooling at the advice of the doctor in attendance because it was thought that such would be a waste of time and money However by good care and good luck he lived to be sixty years old but more important still by sheer will power and genius he educated himself to be one of the leading musical composers of his generation

Heart disease as it affects the community Much that has been discussed under the headings of home school industry business and the professions naturally applies to the community as a whole but there are other aspects of the community that deserve mention One is that of the general standard of living Where there is a low average level heart disease like a good many other diseases is more common It is well known for example that rheumatic heart disease is twice as common in the poorer more crowded sections of a city than in the suburbs where living conditions are better Much the same statement is true about cardiovascular syphilis only still more so Also the circulatory diseases of middle age both peripheral and cardiac are more subject to neglect under poorer conditions of living We do not as yet however have an adequate statistical appraisal of their varied incidence and it

may be that the overnutrition that is more likely to prevail among the well to-do has its influence in the etiology or at least aggravation of the so-called degenerative diseases such as coronary atherosclerosis and hypertension A community sense of responsibility for health conditions builds up slowly but eventually leads to the establishment of a proper health agency in close harmony with private practitioners hospitals and medical schools Some small communities in the country today lack physicians close at hand they should join others in similar plight or perhaps better situated to set up some central group or hospital where someone trained in the field of cardiovascular disease can be available, as in other specialties with essential equipment such as electrocardiograph and fluoroscope

Heart disease as it affects the nation Next to last we come to the problem of the *national health* That *statistically so far as the heart* is concerned will be dealt with in the next chapter but there are a few additional comments to be made here In the first place heart and peripheral circulatory diseases are by far the most common causes of death in the U S A today and so naturally they hold the limelight in the current national health program Fortunately both public enterprise via the new National Heart Institute and National Advisory Heart Council established by act of Congress in 1948 and private enterprise headed by the American Heart Association organized in 1924 are working in close harmony in the support of research and teaching in the field of cardiovascular disease Happily research has the priority for it is evident that the sooner we discover and thereby learn to prevent the underlying causes of heart disease the sooner we shall rescue our young people and middle aged population from cardiac invalidism and death and the less effort time and money we shall need to plan for and expend in their care An increasing mortality from heart disease per se in the years to come need cause no alarm in fact such may be welcomed provided death comes quickly comfortably and quietly while at rest in bed or easy chair at an advanced age say at ninety after a long and happy and useful life But there is still tragedy in the newspaper headlines on occasion when some notable and public spirited citizen suddenly succumbs to heart disease in the very prime of life and at the top of his career

Heart disease internationally Finally the problem of heart disease is world wide and what has been said about its community and national relationships applies equally to all nations An International Cardiac Council was organized in Mexico City in 1946 to help to correlate the various national activities in the cardiovascular field and to aid in setting up the first International Cardiac Congress in Paris in the fall of 1950 At that congress there was established the International Society of Cardiology (Heart and Blood Vessels) There are herein many opportunities for future cooperative researches in the incidence and etiology of heart disease throughout the world and in the strengthening of international medical friendship

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CHAPTER 12

PREVALENCE OF HEART DISEASE AND OF ITS ETIOLOGIC TYPES

The frequency of heart disease The first aspect of the prevalence of heart disease to be considered is that of its total frequency though actually this is much less important than a second aspect to be considered later namely that of the relative and absolute frequency of the various kinds of heart disease dependent on the various causes Accurate information about either the incidence or the prevalence of heart disease in the community is as yet scarcely available anywhere in the world this information is obviously of great importance and much work remains to be done in securing it We possess scattered data of small or limited scope or of uncertain reliability from a number of sources data which are largely incomplete or otherwise unsatisfactory These sources include life insurance statistics periodic health school industrial athletic and military examinations and hospital and mortality figures

The estimation of community prevalence of heart disease has varied from less than 1 per cent to several per cent The reported results of examination of school children have differed widely, but reasonably satisfactory studies in the northeastern part of the United States have indicated that nearly 1 per cent of children of school age have organic heart disease while in San Francisco only 0 37 per cent of cardiacs were found among the school children one half or more of whom had congenital heart disease (Sampson et al 1938) and in Cincinnati the figure was midway 0 53 per cent with 55 per cent of them rheumatic and 45 per cent congenital (Rauh 1939) In 1946-47 Robinson and his associates found among the San Francisco school children 0 44 per cent of cardiacs which when further analyzed, showed 0 24 per cent rheumatic heart disease and 0 19 per cent congenital heart disease However rheumatic heart disease was not at all rare among the children of South California some ten to fifteen years ago as indicated by the finding of 3 per cent of cases at autopsy at the Children s Hospital in Los Angeles among patients through 14 years of age Eighty per cent of the cases at the Children s Hospital were California born (Thompson personal communication 1949)

At the Children's Hospital in Boston in 1949 1 3 per cent of the autopsied cases showed rheumatic heart disease and 10 per cent congenital (there were many infants)

The prevalence of heart disease in school children varies very much with climate because of the greater frequency of rheumatic heart disease in cold wet and high altitude areas for example Sampson et al (1945) reported 2 04 per cent rheumatic heart disease among the school children of Eureka in the extreme northern end of California in contrast to 0 32 per cent of rheumatic heart disease among the school children in Redlands in the extreme southern end of California The incidence of congenital heart disease was approximately the same in both places—0 07 per cent in Eureka and 0 08 per cent in Redlands In 1945 Wedum et al reported among school children in Denver 1 63 per cent with rheumatic heart disease

Among 28 139 young adults entering the University of Wisconsin between 1931 and 1939 there were 289 cases (1 + per cent) of heart disease with sex ratio of 1 7 females to 1 male (Cole 1941) From middle aged adult examinations and from the certainty that in old age the incidence of heart disease is very much higher than in youth it may be stated as probable that at least 2 per cent of the total population of the northern part of the United States have heart disease of a degree sufficient to produce symptoms or signs

As a cause of death heart disease has assumed greater and greater proportions in this part of the world until now it leads all other causes having far outstripped tuberculosis pneumonia and malignant disease the other three most common fatal diseases and also outnumbering accidental deaths which now rank in third place as a cause of death This increase which is absolute as well as relative is due to several reasons the individual importance of which is not yet known (1) more accurate cardiac diagnosis (2) fashions and revisions of recording diagnoses (for example coronary artery disease was classified some years ago under the heading of arterial disease in the Massachusetts state records while now it is classified under the heading of heart disease most persons formerly diagnosed as having Bright's disease are now recognized properly as having hypertensive heart disease with congestive failure and not primarily kidney disease and many persons who died of old age years ago would now be recorded as having died of cardiovascular disease) (3) reduction of incidence of certain other diseases especially of infections like infantile dysentery tuberculosis and typhoid fever with a corresponding increasing ratio of heart disease deaths and (4) actual increase of heart disease due in part at least to this very same decrease in mortality from other diseases Some individuals who in former days would have died of dysentery in infancy of diphtheria in childhood, or of tuberculosis or typhoid fever in early adult life now die of rheumatic syphilitic hypertensive or coronary heart disease instead See Table 2 and Figure 57 [1]

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[1] It is with much appreciation that I acknowledge the valuable assistance of Mr Felix E. Moore Jr., chief of the Biometrics Research Section of the National Heart Institute Bethesda Md in the revision of Table 2 and Figure 57 and for other helpful advice about this chapter

As a background for the increasing mortality from heart disease it is of interest to cite the decreasing death rate in the United States in 1900 the death rate from all causes in the registration states was 1,719 per 100 000 in 1910 it was 1 468, in 1920 it was 1 299, in 1930 it was 1 132 in 1940 it was 1 074 in 1945 it was 1 062 and in 1948 it was 988 The figures for Massachusetts are given in Table 4 It is of much interest that mortality from epidemics has been on the decline in late decades Except for the one serious

Table 2

MORTALITY STATISTICS FOR MASSACHUSETTS, 1900 TO 1945

(Cases allocated to place of residence since 1935)

Year	Death rate per 100 000 population				Total death rate per 1 000 population	Infant death rate per 1 000 live births
	Diseases of the Heart	*Cancer*	*Tuberculosis (all forms)*	*Pneumonia (all forms)*		
1900	165	75	214	172	18 4	*
1905	196	89	192	153	16 7	*
1910	200	94	164	175	16 1	*
1915	201	103	139	159	14 3	101
1920	215	115	114	156	13 8	91
1925	248	124	83	118	12 4	73
1930	282	136	64	93	11 6	60
1935	336	148	46	89	11 5	48
1940	412	169	38	58	11 8	38
1945	44[illegible]	187	39	49	1 2	3[illegible]

Source National Office of Vital Statistics
* Not available on comparable basis before 1915

epidemic of influenza at the end of World War I there have been no increases in mortality from epidemic disease since the beginning of the twentieth century (see Figure 58 for Baltimore)

In previous editions of this book it was stated that approximately one out of every three or four deaths in the U S A at large and in individual areas (such as the State of Massachusetts) was due to heart disease but steadily the proportion has risen so that now if we include all the ramifications of cardiovascular disease including for example renal vascular disease the ratio is very close to one out of two (49 5 per cent) Figure 59 illustrates well the recent data

The accuracy of death certificates is still subject to great improvement but it has gained rapidly during the last generation That the increasing percentage of cardiac deaths is not a unique feature of this country is shown by statistics recently received from France in Lyons from 1887 to 1891 deaths caused by heart disease made up 7 7 per cent of total deaths from known causes while from 1938 to 1940 they made up 17 3 per cent in large part apparently because of the reduction in mortality from other diseases since the actual number of cardiac deaths did not increase proportionately (Paris letter February 7, 1942 *J A M A* 1942 CXVIII 1155) This very increase in

mortality from heart disease provided it comes in old people may be a source for congratulation rather than dismay since it means that life is now being limited by the degenerative lesions of old age rather than by the infections of youth But such degenerative lesions should not appear in youth or middle age The relationship of morbidity and mortality to age is thus a vital one in any consideration of statistics of public health See Figures 60 and 61 on pages 271 and 272

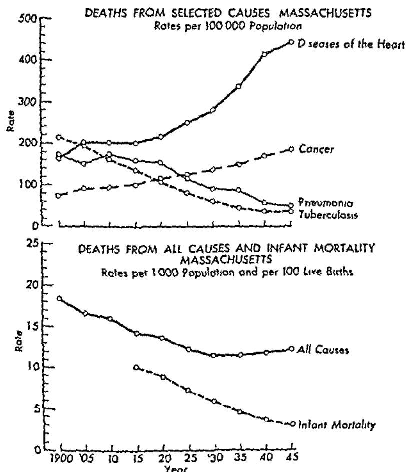


FIG 57 Death rates from diseases of the heart cancer tuberculosis and pneumonia and death rate from all causes and infant mortality rate Massachusetts 1900–1945

It is of great interest that the average duration of human life has more than doubled in the United States of America in the brief interval since its establishment 165 years ago It has been estimated that the average duration of life in this country in 1790 was about 30 years in 1930 it was 58 8 for white men and 62 4 for white women and in 1947 65 16 for white men and 70 54 for white women This greater longevity of females has been con

sistently 4 to 5 years for many decades (Dublin 1933 1941—*Statistical Bull Metropolitan Life Ins Co* 1949 XXX No 10) The expectation of duration of life among the Negroes in the United States in 1930 was 13 years less than that among the whites in 1947 it was reduced to 8 years In 1911 among the policyholders of the Metropolitan Life Insurance Company the expectation of life was 46 6 years and in 1949 less than four decades later it was 67 8 years In some parts of the world where infant mortality and youthful infections are still high the average duration of life is still only in the twenties about as it was probably in Europe in the Roman Era and in

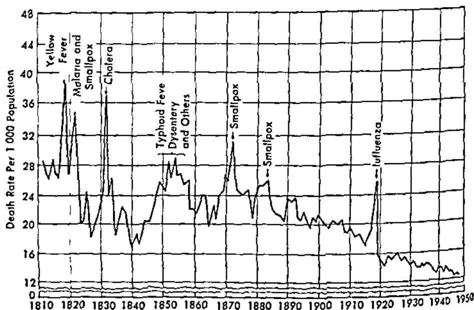


FIG 58 Annual death rates from all causes with indication of principal epidemics, Baltimore Maryland 1812–1948 (Kindness of the Metropolitan Life Insurance Company New York)

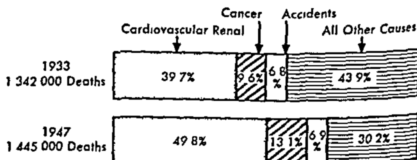


FIG 59 Proportionate mortality from leading causes of death in the United States of America 1933 and 1947 showing the increasing death rate from cardiovascular renal diseases (Kindness of Mr Felix E Moore Jr., National Heart Institute U.S Public Health Service Bethesda Md)

the Middle Ages (Figure 62) However despite the wonderful increase in the average duration of human life in this country in the past century or so the expectation of life for the man or woman who reaches 60 years is no greater now than it was years ago and probably a little less this is a very important aspect of the subject that should receive increasing attention in the future The longest lived persons (centenarians) are in the main those who with a good family inheritance of longevity have lived physically active lives in rural surroundings

Other relationships of morbidity and mortality from heart disease of great importance besides absolute and relative frequency and age are those to

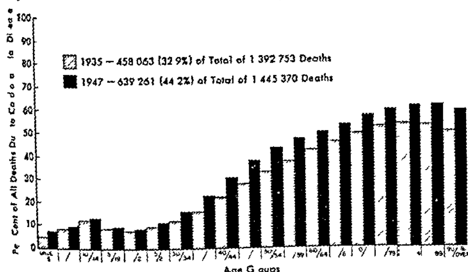


FIG 60 Chart showing total mortality from cardiovascular diseases as compared to all other causes according to age groups in the United States 1935 and 1947 (Kindness of Miss Marjorie Bellows American Heart Association New York City)

climate race heredity sex and social and financial status Favorable influences in reducing the incidence of heart disease in young as well as old are mild dry climates good but not rich food moderate physical exercise and healthful uncrowded living conditions Recently it has been noted that a good environment seems to be more important than having long lived parents in determining the individual s prospect for long life (*Statistical Bull Metropolitan Life Ins Co* February 1942 XXIII No 2) The importance of heredity in cardiovascular disease however is very great perhaps as great as or greater than any other factor but its exact significance remains obscure It has also been found that race is sometimes an important factor Negroes showing twice the prevalence of heart disease as do whites Sex is concerned in three respects in the first place there seems to be a law of nature throughout the entire animal kingdom from insects up to man that the male is considerably shorter lived than the female secondly sex affects the prognosis in every variety of heart disease males living usually a shorter time with any

given heart disease than females, probably in part because of the greater burden imposed by the more active life and thirdly it is related somewhat to the various etiologic types rheumatic heart disease and heart trouble from thyrotoxicosis being found more often in females and coronary heart disease and cardiovascular syphilis more often in males The whole problem of the incidence of heart disease needs however much further study

The causes of heart disease The second and the most important aspect of

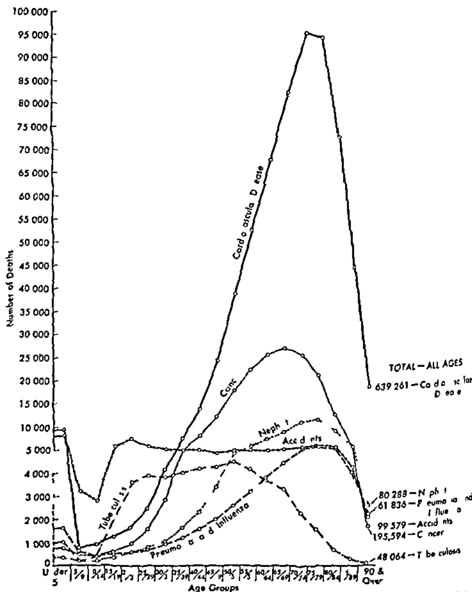


FIG 61 Chart showing total mortality from cardiovascular disease as compared to all other causes according to age groups in the United States 1947 (Kindness of Miss Marjorie Bellows American Heart Association New York City)

heart disease is that of its causes and their relative frequency With the de veloping interest in preventive medicine in recent years there has come the realization of the need of analyzing all disease from the etiologic standpoint Since heart disease is the source of much illness and of high mortality in nearly every community it has attracted much attention and efforts have been made to determine the relative and absolute importance of various factors thought responsible for heart symptoms and signs Preliminary classification of causes and etiologic types of heart disease has begun in several commu nities It holds much promise for the future for it is only as we see the im portance of etiologic factors of disease that we can view them in due propor- tion and concentrate our efforts toward the eradication not only of the most

AVERAGE LENGTH OF LIFE FROM ANCIENT TO MODERN TIMES

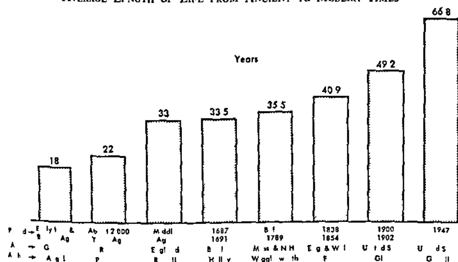


FIG 67 Chart showing the expectation of life from ancient to modern times (Kind ness of Dr Louis I Dublin Metropolitan Life Insurance Company New York Published in *Length of Life* Ronald Press Company New York 1949)

serious pathologic states but also of those most amenable to such an attack in the current state of our knowledge

It is evident that although investigation of many causes of heart disease may well be carried on at the same time by workers all over the world the wisest course is to concentrate in any one community on that community s own particular causes most in need of control or most obviously open to attack In New England the rheumatic infection hypertension and presenile coronary disease are the most important factors now demanding study Many years will elapse before we are left with the problem of old age alone Mean while the practitioner of medicine may himself contribute to the progress either by concentrated study of some particular etiologic factor or factors or, in a routine way by recording as accurately and faithfully as possible in every patient with heart symptoms or signs the causes whether clear doubtful or

unknown Gradually in this way will come a better realization of the problems which lie before the medical profession in this large and important field

Lest it be thought that the effort of classifying each cardiac patient according to etiologic type is superfluous or an idle fancy of a public health Utopia I would hasten to add that for the individual patient himself the method is also of great value Accurate diagnosis prognosis and treatment may depend entirely on the recognition of the cause of trouble it can definitely be said that the etiologic diagnosis is often more important than that of either structural change or functional condition Congestive failure (myocardial insufficiency) and angina pectoris (coronary insufficiency) are of course of prime importance to recognize and treat as functional disorders but we can handle these cases much more intelligently if we know the fundamental cause of the disease back of their insufficiency For example congestive failure complicating coronary occlusion is more serious as a rule than that due to chronic mitral stenosis and angina pectoris in syphilitic aortitis is more significant than that in rheumatic aortic regurgitation in youth or in mild form in the coronary disease of old age

There are changing fashions in medical diagnosis A generation or two ago it was considered sufficient to ascertain the pathologic alterations present in the way of structural damage in the heart and textbooks were filled with a discussion of valvular lesions and myocarditis Then came a step forward when greater emphasis was placed on the functional state of the circulation than had been done before (Mackenzie 1908) This emphasis was much needed and served an important purpose but there has been a strong tendency as a result to make too light of the structural defects and indeed hardly to bother to look for them in detail The pendulum swung too far but there is now fortunately reappearing a growing respect for the lesions in the heart that can themselves serve as sources of strain and failure or that point to other disease processes or to other sources of strain in the body We must not think too little of either functional disorders or structural changes we must seek them all and make note of them at least those of most importance in cardiovascular diagnosis A functional disorder like paroxysmal tachycardia sometimes may be alarming but it is usually unimportant and far less significant in diagnosis than is mitral stenosis On the other hand a slight chronic rheumatic aortic regurgitation is far less important than is the serious functional disorder of angina pectoris

It is with the newest element of cardiac diagnosis the etiologic factor that this part of the book will deal This element has long been more or less recognized as of some importance but only in the last generation has it been emphasized properly (Cabot 1914) The following quotation represents a milestone in the progress of our study of cardiovascular disease

Cabot R C 'The Four Common Types of Heart Disease *J A M A* 1914 LXIII 1461

To classify cases of disease according to their pathogenic agent or process

and not solely by naming the region affected or the function disturbed is the ideal of scientific progress in medicine

"But until the last decade we have made little advance in this direction as regards the diseases which gravely disturb heart function Thus we still find in standard textbooks a section devoted to mitral regurgitation its diagnosis prognosis and treatment although mitral regurgitation is almost as vague a phrase as spinal paralysis or brain fever Just as a spinal paralysis may be due to trauma to the tubercle bacillus to the Spirochaeta pallida to the organism of poliomyelitis or to cancer so mitral regurgitation is only a symptom caused by the action of streptococci by the degenerative lesions of arteriosclerosis by the muscle tiring resistance of nephritic hypertension and probably by many other causes

"A similar criticism applies to all diagnoses of myocarditis The micro organism of rheumatism and of syphilis the ravages of arterial disease and perhaps many other causes may produce the lesions of chronic fibrous myocarditis with or without recognizable symptoms A diagnosis of myocarditis is like a diagnosis of ulcer it calls for an etiologic qualification such as syphilitic or tuberculous

The matter has many practical aspects A sane prognosis and treatment of aortic regurgitation for example depends on knowing or guessing what disease has produced it Even physical diagnosis may have to await an intelligent interpretation of its results until we make up our minds what micro organism is at work in the heart as well as elsewhere in the body

While we should thus emphasize etiology and consider it first and generally foremost we must not lose sight meanwhile of the other two legs of the tripod of cardiac diagnosis structural change and functional condition All together the three elements complete satisfactorily our modern idea of analysis of a cardiac case Th represents another step in our progress and a sound one built upon the experience of the past and of the present Instead of diagnosing simply mitral stenosis or atrial fibrillation or rheumatic heart disease in a given case we should make the complete diagnosis of rheumatic heart disease (etiologic) with mitral stenosis (structural defect) and atrial fibrillation (disorder of function) (White and Myers 1921)

Heart disease may be very complicated Not only are there many different causes of trouble but two or more of these separate causes may occasion trouble simultaneously in the same heart and in different and even inconstant degrees Often much study and discernment are necessary to judge the relative responsibilities of several different causative factors in a given patient and in some cases it may be impossible to unravel the tangle In this volume the combinations of etiologic factors that are most common or important will be indicated in the discussion of complications in each chapter

In the present part of the book the more important causes and etiologic types of heart disease will be given by chapters chiefly according to age prevalence since that is a very practical arrangement leaving for later consideration certain factors of but slight or doubtful importance or of extreme rarity This plan seems better than that of arrangement according to importance or frequency because it leads one chronologically through the life history of man and because the various factors are of different prevalence and importance in

Table 3—THE RELATIVE PREVALENCE OF THE VARIOUS ETIOLOGIC TYPES

Et ologi Types f Heart Disease		USA (a a g d alphalet c lly) ALABAMA, W f h a d Porter 1948 2 418 ases 1 406 wh t 1 012 N Wh tes bovel \ g, o l t 1936 1946	CALIFO IA (Sa Fran isco) G ger t l 1936 3 535 ca es	COLORADO Da h 1939 701 ca es m ng 14 6/9 hospital dmi o s (4 8) in D er	ILLINOIS Fio man 1934 Cook County Hosp tal Ch cag 1 646 ases (1932 to 1933) bo e h vyl e Wh tes abo e 6 e l e N g oes below Moher S iller nd Lil H 1935 Ch go 1 000 c es below h avyl e	IOWA Myer 1927 Above l 510 c e out f t tal of 1 000 w th a dia symptoms r K s R th nd Paul 1933 B l w l ne 1 329 c ses U ers ty H t l l w City 1925 to 1931	LO ISIA A Holoubek, Holoubek d B ker 1947 8 313 a t p Char ty H t l 1045 r t d w se Wh t bo e N groe b l w	M N SOTA Cl w 1941 4 678 [illegible] 10 265 a topsies
Co g t l nom l s		3 3% 2 3	5 5%	1 7%	— 0 0	2% 2 0	1 3 9	—
Infecti	Rheumati type	11 5 14 5	22.2	24 8	19 0 10 4 24 2	36 0 2 3	4 74 0 3	15 6
	S bacut bact ri l endocarditi	0 2 0 5	0 9	5 4	2 9 2 1 1 0	1 0 1 6	.86 6	11 0
	Acut bact ri l ndocarditi						33 17	
	Card ascul r syphili	0 9 5 8	7.[illegible]	2 6	8 27 1 9 5	5 0 6 2	2 55 15 6	7 0
	Oth s, i cl d g diphth t be culosi th viruses a d oth r f t tion						1 24 .60	—
Thyrot xicosis			2 9	0 5	3 0 1 6 9 3	1 5 8 7	— 4	0 1
Hypertens n	Sy tem c Hyperpies	55 62 4	21.5	30 4	53 6 60 4 26 2	24 5 34	12 35 28 13	53 5
	Pulmon ry C pulm nal	0 9 0 7	0 9	0 9	2 1 0 2 3 8		— 0 4	1.5
C ro ry th rosclerosi (l di g cases with angi pect ri)		5 8 5 7	33 6 n m (1 ted 24 9)	17 3	21 1 8 5 24 1	32 5 15 4†	12 3 6 4	25 9
M scell eous—T c states, tr um tum s, t		3 5 6 8		6 4	1 3 1 0 —		1 0 1 0	—
U known		1 0 1 4			2 3 0 —	4 5 2	— 2	—

†Ex l d g those cases w th hype te si n

NEW ENGLAND [illegible] 1 28 2 421 [illegible]	[illegible] 1951 [illegible] 3 000 [illegible]	NEW YORK CITY [illegible] 1926 1 001 [illegible]	NEW YORK STATE [illegible] 1933 1934 [illegible] by 296	OHIO [illegible] 1941 790 [illegible] 6 548 autopsies [illegible]	OHIO (Cl[illegible]) [illegible] 1935 1940 [illegible] 1948 2 000 [illegible] 80% [illegible] 20% Negro [illegible] 49 2% [illegible] cardiac cases	OREGON [illegible] 1929 96 [illegible] 1 344 [illegible] below the line [illegible] as above the line [illegible]	PACIFIC NORTHWEST [illegible] 1935 556 [illegible]	ROCKY MOUNTAIN [illegible] 1930 867 [illegible] total of 1 000 [illegible]	TENNESSEE [illegible] 1933 645 cases [illegible] University Hospital [illegible] White [illegible] Negroes below line	TEXAS [illegible] 1927 [illegible] 915 cases (501 [illegible] 414 Negroes [illegible] 1931 [illegible] 1 660 [illegible] (whites [illegible] Negroes)— [illegible]	VIRGINIA [illegible] 1926 700 cases [illegible] 112 Negroes	WEST VIRGINIA [illegible] 1932 118 cases	WASHINGTON D C [illegible] 1933 [illegible] 1 000 cases (400 white [illegible] 600 Negroes below) [illegible] 1935 Below [illegible] 450 [illegible] cases [illegible] in 1932 258 whites above line [illegible] 192 [illegible]
1 5%	7 9	0 7%	2 4%			0 1% / 0 %	0 9%	1 1%		1 0% / 0 2%	1%	0 8	— / 2 3% / 1 %
39 5 (4% hospital and 30 pr[illegible] t)	23 5	45 8 / 25 5	27 2	15 1	12 0	13 / 11	20 0	44 0	15 3 / 4 3	10 4 / 3 6 / 4	22	3	2 / 4 7 / 1 1 / 8 3
1 9	1 2			3	13% among [illegible]	— / —		0 2		1 8 / 1 2 / —			1 8 / 1 0 / 5 4 / 3 6
Ra e	Ra	0 5	—	1		— / 2							
3 9	1 0	9 3 / 5 0	4 6	8 5		5 / 4	2 0	1 1	15 4	9 2 / 31 6 / 12 7	11	1 6	4 3 / 15 5 / 5 0 / 21 3
Ra	R												
2 9	0 5	1 1		1 1		11 / 4	2 0	9 3		1 4 / 1 2 / —	31	5 9	3 / 1 2 / 0 8 / 2 1
29 2	26 2	1	20 1	33 4	27 6	70 / 38	49 4	14 9	65 1 71 8 combined	45 3 / 50 5 / 57 2	46	44 9	51 4 / 59 2 / 6 1 / 56 3
0 9	1 1	0 5		6 8					↑				↑
3 7	48 5	arteriosclerotic 18 4 / 43 5	8 8	22 4	51	17 / 21	20 3	21 1	↑	24 0 / 6 3 / 20 2	46	9 3	26 0 / 13 3 combined
2 1	1 7	t[illegible] m 0 1		4	9 4	— / 3	5 4	0 9		1 4 / 1 2 / —			
3 4	0 6	19 5 / 8 1		2 4		— / 8		7 3		5 6 / 4 1 / —	2		

19 ½ pe[illegible] t [illegible] f th[illegible] pr[illegible] t pat[illegible] [illegible] h[illegible] d [illegible] g[illegible] pe[illegible] t [illegible] d only 9[illegible] pe[illegible] nt of th[illegible] hospital case

Table 3—Continued

	Et olog c Types of Heart Diseas	Hawaii B k d H fuell 1949 81 949 med al dmiss ons 1 2f9 d c jat t	Puerto Ri o S a 1945 (1937 1944)	**OTHER COUNTRIES** (a ra ged alphabet c lly) Arg ntine Republic C 1943 10 000 a d ac pat e t (6 000 h t t 1 4 000 pri te) B uos A res	Con al S b th 1943 4 500 c ses (3 000 hospital 1 500 pri ate) R n	C l o-4 b ne 1943 3 594 ses (3 279 hosp tal 315 pri at) M d s	B azil (J 1 Cea 1948 438 ses	Rio J N o M l 1948 3 664 pat t I f of C d 1 ey 2 050) nm l cases
	C ngenit l n m lies	3 7	1 0	2 4	2 5	1 5	1 5	3 61
Infect	Rh mati type	17 3	17 4	18 2	18 4	23 0	9 3	9 3
	S b cut b t ri l ndoc d t	15						
	A ut b te al e doc dit s							
	C d ov cula yph li	2 2	6 1		9 0	6 8	14 3	13 5
	Oth l d g d phth ri t be los ru es a d oth nfestat	23						
	Thy t cos	55	6	3 8	3 3	1 2	1 1	
Hypert	Sy t mi Hype pies	32 2 Hype & C 8 8	22 8	23	20 0	23 0	45 2	23 5
	P lm ry Co pulm l	23		3 3	1 6	0 9		
	Cor ry th osclerot t l di g ses th gi pe tori)	33	39 9	29 6	36 4	39 6	26 9	31.3
	M scell eo —t t tes t ma t m rs t	1 7	10 2	8 9	8 8	2 0	1 3	16 8
	U k	15					4	

By personal commu cati n t Cossi (1943)

B (C) S o P in *Landal(J* l al 1 4 1 21 pa ie mi l ll 1 44 (be) 4 105 pa l yr 1 shes (be)		13.1 / 15.6		3.6 / 10.7		3.6 / 10.1	33.6 / 36.8	1.7 / 2.0	19.5 / 16.5	6.2 / 7.2	1.9 / 4.6	
S a P o. R m l) 49 (t h f l f nt (457 c) (al) p t l n (003) (b low)	0 / 1.0	21.0 / 1.55		18.2 / 2.6	0.4 / —	1.1 / 1.2	23.7 / 67.6	5.5 / 1.3	17.3 / 5.5	2.4 / 1.2	7.0 / 0.6	
Les *Cuneva* d 1933 855 cl d g 4 5 1 m the C l mbo C l Hosp tal ab } nd 400 pri te pat L l w l	1 / —	20 / 8	2½ / —	10			13 / 25		2½+ / 10+	many w th se er An mia		
C lom ia *Sal do-Sulz* 1947 3 2 p l at pat 1 n B ia	2.1	8.4	0.9	7.2		3.0	36.1	3.8	25.0	33.5		
Costa Ric G *C rrilla* 1949 8 000 a t j Mo t l ty 9 6 a d o ase) r d sease	3.61	9.3		15.5			3.5		31.3	16.8		
E l n C md 19 6 1 000 pat nt Hosp tal es bo e l t l t pat ts bel w l e	2.0 / 2.7	51.0 / 25.0	1) / 6	9.0 / 4.0		4.0 / 2.7	d o- / 0 / 8.6		sen l 10.0 / 41.0		6.4 / 7.9	
F Nce *Leneg* d *Kil d* 1949 J P h sp t l pe l ng h rt lisea.	8	29.2		9.2			2? 8	5	32.4 (17.4 with combi n ti)	1		
I s I k 1949 10 104 medic l pati nt		38					41.3		20			
M x o ( ) er 1941 1,674 p t pati t bo h nt 716 h sp t l pat t bel w l	2.0 / 1.2	32.1 / 61.5	0.5	8.8 / 16.9		2.0	18.4 / 2.6		32.9 / 17.6	3.0 / —		
N rw y *Ormk* g 1921 577 ase 58 m abo h 289 om n b low lin)		44.1 / 57.6		12.2 / 4.2								
South Africa *H m and o* ec les 1929 153 Eu o pe s (mostly Kaff rs)		41.8	9.1	5.5 (ma y a cu ry m)			some t m (? m- be)		16.3			
S ain (M t h *Ort* 1 *q* 1949 19 0 1 000 c t se (abo 1 000 nsec t a tops 2 l osp t l bel)	2 / 1.5	5.5 / 34.5	3 / —	13.1 / 8	— / 3.4	8.8	5 / 11.1	3.3 / 0	5.9 / 1.4	13.8 / 9.4		
A Ska 4 berg 1937 485 sa) rs (49 uht		21.3		11.7			41		18.0	4		

different parts of the world In New England for example rheumatic heart disease makes up an imposing percentage of all types put together and syphilis as a factor is relatively unimportant, while among the Negroes in the South rheumatic heart disease is far less common and cardiovascular syphilis far more frequent It is still too early to give satisfactory figures for the prevalence of etiologic types in different parts of the world only a few studies have been made which allow certain comparisons and these are not always parallel The surface has hardly been scratched A large amount of international cooperative research along these lines deserves early priority

I have tabulated on pages 276 to 279 the etiologic types of heart disease listed according to age incidence which may be found helpful as a guide to further study In this list will be found figures of percentage prevalence of the various types reported from New England New York Washington DC and several states of the South Middle West the Rockies and Far West in the United States and from England Norway South Africa Colombia Mexico the Argentine India, and the high seas The figures are often inadequate and of limited value but they are the best we possess today slowly they are increasing in number and accuracy (see Table 3 pages 276 to 279)

Finally we must at present leave a space in our classification entitled 'of unknown cause this is still an important group varying in different localities from about 1' or 2 per cent up to 15 or 20 per cent This very acknowledgment of our ignorance should act as a spur to us in our studies until eventually we may be able definitely to say we do know all the causes of heart disease With that knowledge there is bound to come more opportunity to prevent heart disease Incidentally there is an enormous miscellany of diseases which may depress the circulatory function or slightly or terminally alter the heart or the blood vessels (see the end of Chapter 23) but which do not deserve the designation of types of heart disease

To add important and useful information about heart disease in order to help fill the many and serious gaps in our knowledge has required the concentration of many workers in the past three or four decades especially since World War I (1914–1918) These men and women who have become specialists in this field have advanced our knowledge about cardiovascular disease further in that short interval of time than it had traveled in all the centuries that had gone before when few doctors had the interest or took the time to study the heart and circulation either in the normal man or in the cardiac patient This book which is largely a record of the work of the hundreds of students and investigators of cardiovascular disease since 1900 is a testament to that truth

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CHAPTER 13

CONGENITAL CARDIOVASCULAR DEFECTS

Introduction Congenital defects of the heart and blood vessels though not frequent comprise one of the most difficult important and interesting medical problems of our day More progress has been made in our understanding of their clinical significance and in their recognition during the last two decades than in any other type of heart disease the successive editions of this book which were begun just twenty years ago illustrate this well Also considerable and spectacular advances have been made in the surgical correction and amelioration of several of these defects and intracardiac catheterization has been applied especially in this field Table 5 (page 294) presents in summary th current clinical status of the congenital defects of the heart and great vessels Less important extremely rare or as yet undiagnosable defects are not included in this table but are for the most part mentioned in the listing of 1 000 autopsied cases collected and classified by Maude Abbott Because of its historic interest and value pathologically her classification and figures have been retained in this edition but the tabulated insert has been omitted

Mention need be made herewith only of two rare anomalies incompatible with life namely acardia (absence of heart) and hemicardia (absence of half the heart) these conditions were reported by Maude Abbott in 15 cases of an early series of hers of 850 autopsied cases (1928)

Incidence We still await adequate statistical information about the absolute and relative incidence of congenital cardiovascular disease in various parts of the world Our current impression is that it is found everywhere and in about the same total incidence but that it varies a good deal relatively depending on how much heart disease there is in general and so far as children are concerned on how much rheumatic heart disease there is in any district or community Statistics already available but as a rule still crude indicate a low total incidence averaging well under 1 per cent of all deaths An analysis of 34 023 unselected autopsies in Boston showed congenital cardiovascular disease in 1 33 per cent but this figure dropped to 0 5 per cent after the age of two (Gelfman and Levine 1942) An incidence of 0 9 per cent of con-

genital heart disease among 15 597 autopsies was reported by Clawson (1944) of this lot of 141 infants 18 were stillbirths and 83 died in the first five months of life only 30 cases (21 3 per cent) surviving after their first year A clinical series of 31 771 medical outpatients in Copenhagen contained 85 cases (0 27 per cent) diagnosed as congenital heart disease among 4 746 individuals with cardiovascular abnormalities (a relative incidence of 1 8 per cent) (Thordarson 1947) In a clinical series of cardiac patients under the age of twenty years in New England 6 per cent were found to be of congenital origin (White and Jones 1928) this figure would doubtless have been higher had more young infants been included since many of those severely involved die very young In California some years ago (1936) it was noted that the ratio of congenital to rheumatic heart disease was very different from that in New England being very much greater recent statistical information confirms the earlier figures among San Francisco school children there bein 0 19 per cent with congenital heart disease and 0 24 per cent with rheumatic heart disease a ratio of about four to five while the ratio in New England was once about one to ten until recent years when with the decrease of rheumatic heart disease and the increase of congenital cardiovascular cases seeking help the ratio has changed in New England to about two congenital to three rheumatic (actually 165 of the former and 257 of the latter under the age of twenty years among 2 000 cardiac patients—White 1951)

Etiology *Cause* One of the three great advances in our knowledge of this kind of heart disease during the past decade not known when the third edition of this book was being prepared has been the first clear evidence of a causative factor the other two advances being more accurate diagnosis and surgical treatment respectively In the last edition certain guesses were mentioned including alcoholism syphilis trauma fetal endocarditis and defects in the germ plasm but there was no clear knowledge It is still quite possible that some of these factors and others not mentioned or even thought of may prove eventually to play a role but the one substantiated factor discovered in Australia a few years ago (Gregg 1941 Swan 1943) was not mentioned earlier This is German measles (rubella) a virus disease, which appears to result in a combination of congenital defects (cataracts cardiovascular anomalies and at times deaf mutism and mental maldevelopment) in a considerable percentage of instances in which the mother is affected during the first two to three months of pregnancy The exact percentage is not yet known but has been to date estimated to be from one quarter to one half of the cases or even more One of the most recent reports (Wesselhoeft 1949) cites 67 infants with congenital heart lesions born of 132 mothers who had had rubella during the first trimester of pregnancy More recently other viruses have been suspected of causing congenital defects of heart and aorta in the fetus during early pregnancy but accurate information about this is still lacking

Our newly acquired knowledge about rubella and congenital heart disease gives us our first real hope about preventative measures At present the first crude steps have been taken in the way of advice to terminate pregnancy if rubella occurs during the first trimester or to attempt to infect girls and

young women before marriage but of course the vital need is early cure and prevention of the viruses themselves Gamma globulin has been suggested but its value has not been substantiated as yet in the case of rubella

Not rarely the apparent scarring with fibrosis and contraction of the endo cardium of the right ventricle involving especially the infundibular area and the pulmonary valve itself strongly suggests the possibility of fetal endo carditis If this should be proved to be true we may again have weapons against such involvement in the form of modern chemotherapy and penicillin and its like in fact it will be of interest to determine whether in the future there may be a decrease in the incidence of infundibular and pulmonary stenosis associated with the current extensive use of these new therapeutic agents during pregnancy On the other hand the white fibrotic thickening of the endocardium per se as in the case of congenital anomalies of the coronary arterial circulation (in particular when the left coronary artery arises from the pulmonary artery) is ascribed best to the effect of prolonged anoxia

Sex There is a curious relationship of sex in certain congenital cardio vascular defects In the largest series of cases on record (1 000 cases with the sex stated in 859 Abbott 1931) the ratio of males to females was 58 to 42 it happened that in some of the individual lesions of this series the sexes were about evenly divided but pericardial defects (21 males to 9 females) cor biloculare i e two chambered heart and triloculare i e three-chambered heart (17 to 10) defects of aortic septum (28 to 11) transposition of arterial trunks (42 to 18) anomalies of the semilunar valve cusps (32 to 5) and coarctation of the aorta (60 to 19) were much commoner in the male while simple patency of the ductus arteriosus was more common in the female (55 to 29) and in the 53 cases of true atrial septal defect studied by Bedford Papp and Parkinson (1941) there was a female preponderance of 4 to 1 more cases however are needed to allow one to be at all certain of these pro portions Recently the large series of cases of ductus patency operated upon by Gross (personal communication January 1950) gives a ratio of 276 females to 120 males and of coarctation of the aorta by Reifenstein et al (1947) gives one of five males to one female

Age Congenital heart disease may be found at any age but it is commonest of course in the infant and young child because many of the victims survive but a few years at the most and often only a few days or months The diagnosis is much more difficult however in very young children than at an older age because of the absence or paucity of symptoms and signs this explains why the percentage of accurate clinical diagnoses can be and often is higher in general hospitals than in children s or infants hospitals The age to which the patient lives depends largely on the degree of cyanosis and on the size of the heart markedly cyanosed children and those with very large hearts rarely survive to adolescence or to full adult age or at most beyond 30 years Delay in closure of a ductus arteriosus or of a foramen ovale during the first few months of life should not be interpreted as abnormal

Race Congenital cardiac defects have been reported in every civilized race they do not seek any particular country or climate

Social status Favorable social status and financial resources have not yet been shown to prevent congenital heart disease but they do favor longevity

Pathology The individual defects found in congenital heart disease will be discussed later in this chapter The most common defects in Abbott s post mortem series of 1 000 cases are interatrial septal defects (373 cases) inter ventricular septal defects (274 cases) simple patency of the ductus arteriosus (242 cases) pulmonary stenosis (151 cases), anomalies of the cusps of the semilunar valves (146 cases) coarctation of the aorta (adult type) (105 cases) anomalies of the great veins (94 cases), and complete transposition of the arterial trunks (74 cases)

Cases with combined cardiovascular defects are more common than those with the individual defects alone This is particularly true of interatrial septal defects pulmonary stenosis interventricular septal defects and patency of the ductus arteriosus In Abbott s series of 1 000 cases mentioned above an atrial septal defect was noted as the primary lesion in but 73 cases while it com plicated other lesions in 300 cases, interventricular septal defects were classi fied as the primary lesion in 55 cases and as a complication of other lesions in 219 cases simple patency of the ductus arteriosus occurred primarily in 92 patients and as a complication in 150 others, and pulmonary stenosis occurred alone in but 9 cases while it was combined with other defects in 142 cases As a matter of fact it is to be expected that the defects should be complicated either through the simultaneous involvement of several areas of the heart in the embryonic maldevelopment or through the pressure effects secondarily re sulting from a single lesion like pulmonary stenosis aortic stenosis or tri cuspid atresia (complete closure) to keep patent the ductus arteriosus and defects in the septa between atria and between ventricles Only in certain in stances as in the case of pericardial defects of primary congenital hyper trophy and of coarctation of the aorta do the defects tend to be isolated rather than in combination

The stage in the development of the embryo at which retardation or abnor mality of growth occurs determines largely the type of congenital heart disease found later If the abnormality comes relatively early before the septa have appeared or have grown appreciably, the heart may remain as in the case of the primitive vertebrate heart (that of the fish) with but one atrium and one ventricle (cor biloculare) if the defect in growth begins later the heart may be three chambered as in the case of the reptile with two atria and one ven tricle (cor triloculare biatriatum) Much less commonly the three-chambered heart has two ventricles and one atrium (cor triloculare biventriculare)[1] Later in the stage of embryonic growth after the septa have almost completely formed a defect may cause a permanent opening in the interatrial septum (which may be either a patent foramen ovale or a persistent ostium) or an aperture at the base of the interventricular septum just anterior to the unde-

[1] A unique freak of nature has been reported by Sinclair (1944) of a five-chambered heart with two atria a right ventri le and two left ventri les in a two-headed human monster with two aortas and two pulmonary arteries

fended space Also at this stage or earlier the common truncus arteriosus may not be completely divided into aorta and pulmonary artery leaving so called partial or complete defects of the aortic septum If in the course of growth of the embryo there is either (1) reversed torsion of the ventricular bend of the embryonic heart (2) malposition of the aortic septum in relation to the interventricular septum or (3) incomplete involution of the aortic part of the conus a transposition of the great vessels may result the aorta arising from the right ventricle and the pulmonary artery from the left

In the explanation of transposition of the great vessels in particular Spitzer s important phylogenetic theory deserves a leading position (1923) Harris and Farber (1939) have written about it as follows

Spitzer s main contribution is a theory of normal cardiac development The fundamental postulate of that theory is the orderly development of the organ as a unit in response to the varying conditions forces and demands in a series rising *from fishes to birds and mammals It admits of no fortuitous variations which* disregard the phylogenetic interrelations of these groups

With the advent of pulmonary respiration in phylogeny a very much greater volume of blood must pass through the heart Bending alone becomes inadequate to compensate for the lengthening tendency and torsion must take place The original right bend initiates the torsion to the right and the bulbar elements are thrown into a clockwise spiral Since the heart is fixed at both ends detorsion must take place and a counter clockwise spiral must be present at the opposite or venous end

"According to Spitzer this is the most important stage in cardiac development *Without it no advance could take place with faulty degrees of torsion the most bizarre anomalies result* The concept of torsion recur repeatedly through Spitzer s hypothesis and its importance cannot be underestimated The septum formation must not only separate the pulmonary and systemic circuits but also cross the circuits so that systemic venous blood enters the pulmonary artery and oxygenated blood passes out through the aorta A straight septum could only cause the circuits to exist side by side as in cases of complete transposition Torsion conditions the necessary spiral at the arterial end and thus permits the crossing over of the circuits In order that the countertorsion may not undo this effect the countertorsion must take place *peripheral* to the entrance of the pulmonary veins Furthermore it is through the torsion that the course of the longitudinal folds along which the blood flows easily is directed more or less into the current The forces residing in the blood stream may then work on the folds stimulate them to grow and cause them to develop into septums

A failure in development of the conus arteriosus or perhaps an infection involving it or its valve cusps after it has become differentiated into the infundibulum of the right ventricle results in pulmonary valve or oftener infundibular stenosis or atresia If this stenotic defect comes late it may occur as the only ventricular abnormality but this rarely happens generally it develops early along with failure of the interventricular septum to close completely with diversion of the blood into the aorta from the right ventricle in

a variable but usually considerable degree In most of such cases the aorta is dextroposed overriding in varying extent the ventricular septal defect and best explained by Spitzer s theory It is this combination of pulmonary stenosis interventricular septal defect dextroposition of the aorta and hypertrophy of the right ventricle that is more commonly found than any other cardiac condition in children (over a year old) and adults with cyanosis resulting from congenital heart disease This is the so called tetralogy of Fallot described by Stensen (Steno) in 1672 Sandifort in 1777 Hunter in 1784 Farre in 1814 Gintrac in 1824 and Peacock in 1858 but analyzed more completely as a clinical entity by Fallot in 1888

Fallot A Contribution a l anatomie pathologique de la maladie bleue (cyanose cardiaque) *Marseille med* 1888 XXV 77 138 207 270 341 and 403

Fallot s conclusions are as follows (translation by myself)

1 Clinicians have until now considered the precise diagnosis of the anatomic lesions of congenital heart disease with cyanosis (la maladie bleue) as almost impossible and to be expressed in the form of an entirely vague and uncertain hypothesis From observations that we have assembled it appears on the contrary that congenital heart disease with cyanosis above all in adults is the result of a small number of perfectly definite cardiac malformations

2 Of these malformations there is one which in frequency surpasses all others since we have met it in almost 74 per cent of our observations it is this malformation then that the clinician will be justified in diagnosing and in so doing the chances of error which he will run will be relatively few

3 This malformation constitutes a true pathologic anatomic type represented by the following tetralogy (1) stenosis of the pulmonary artery (2) interventricular septal defect (3) deviation of the origin of the aorta to the right and (4) hypertrophy of the right ventricle almost always concentric in type At times there is an additional entirely accessory defect namely patency of the foramen ovale

4 One cannot at the present time attribute the maladie bleue to the persistence of the foramen ovale without direct opposition to the great majority of observed facts when the communication between the two auricles exists alone without any other associated cardiac lesion cyanosis does not result

5 From the historical point of view one finds in the writings of the last century (the eighteenth) and of the beginning of the present frequent observations of congenital heart disease with cyanosis the majority present the interesting combination of the various cardiac lesions mentioned above

6 Finally from the pathogenic point of view the theory that considers the interventricular communication as a simple phenomenon belonging to the group of recessive anomalies rests only on a superficial and inexact interpretation of the facts the incompletely developed septum in the victim of the maladie bleue can be considered in no way as the analogue of the false septum of vertebrate animals with communicating ventricles it appears much more logical and more in keeping with physiological laws to regard the entire series of cardiac anomalies enumerated above as the consequence of the stenosis of the pulmonary artery As to the cause of this pulmonary stenosis we believe that we should attribute it not to a simple arrest in development but rather to a pathological process occurring in the region

of the pulmonary valve and of the infundibulum just below it during intrauterine life"

Much rarer than the tetralogy of Fallot is another somewhat similar combination of congenital defects consisting of dextroposition of the aorta (which is quite likely the primary condition as indeed it may be also in the tetralogy of Fallot) interventricular septal defect large right ventricle and normal or increased size rather than stenosis of the infundibulum and pulmonary valve and artery (Eisenmenger 1897 Rosedale 1935) A new entity associated with persistent cyanosis from birth with clinical fluoroscopic and electrocardiographic findings very similar to Eisenmenger s complex with which it is likely to be confused has been recently described by Taussig and Bing (1949) This new entity includes transposition of the aorta and a partial overriding of a ventricular septal defect by the large pulmonary artery arising primarily from the right ventricle

Finally of the commoner defects coarctation of the aorta and permanent patency of the ductus arteriosus appear latest of all at birth or shortly after when the heart and great vessels have otherwise attained normal growth and relations they may then occur alone probably because they are late defects Patency of the ductus arteriosus may really be designated as a postnatal defect since normally the ductus does not close until the first few days weeks or months after birth the ductus arteriosus was closed before the age of 8 weeks in 88 per cent of 558 normal infants hearts and the foramen ovale prior to 12 weeks after birth in 87 per cent of this same group (Christie 1930) Recently Everett (personal communication 1951) has found that the foramen ovale closes sooner after birth considerably before the ductus arteriosus

Clinical classification of congenital cardiovascular disease Various attempts have been made to group the different congenital cardiac defects and their combinations in order to produce a useful clinical classification not following necessarily any embryologic or pathologic plan A classical arrangement is that of the division of the cases into three groups (Abbott 1924 1928 1936) this arrangement is shown slightly modified in details in the following plan It may be said that the greater the degree of cyanosis the more serious is the case

Table 4

CLASSIFICATION OF CONGENITAL CARDIOVASCULAR DISEASE (ABBOTT)

(Order based on degrees of oxygen unsaturation and duration of life in 1 000 autopsied cases analyzed by Abbott)

I *Cases without Abnormal Communications or Shunts between the Right and Left Sides of the Heart Acyanotic Group* The lesions of these cases cause varying degrees of cardiac strain from little or none to a great deal Here belong the following relatively unimportant defects as well as more important anomalies

A Less important group

1 Simple dextrocardia usually with the situs inversus No limitation of life unless there are other congenital cardiovascular defects

2 Anomalies of the pericardium Defects and diverticula Maximum age = 75 years mean age at death in 36 cases = 45 years

3 Anomalous chordae Maximum age = 84 years mean age in 23 cases = 43 years

4 Uncomplicated quadricuspid and bicuspid semilunar valves more often aortic than pulmonary bicuspid aortic valves are a frequent site for bacterial endocarditis and so cannot be considered to be wholly unimportant Maximum age = 80 years mean age in 44 cases = 34 years

5 Double atrioventricular orifices Maximum age = 71 years mean age in 9 cases = 37 years

6 Pure coarctation of the aorta of adult type Maximum age = 92 years mean age in 70 cases = 33 years

7 Anomalies of aorta (such as right aortic arch) of the aortic branches of the coronary arteries of the pulmonary arteries and of the great veins unless these are extreme Very variable duration of life but as high as 87 years with double aortic arch (and as low as 3 months with left coronary artery arising from the pulmonary artery)

B More serious group

1 Ectopia cordis (extrathoracic heart in the abdomen) extra abdominal ectopia cordis does not allow survival for more than a few days Maximum age = 15 months mean age in 7 cases = 1 month

2 Primary congenital hypertrophy of the heart Maximum age = 4 years mean age in 15 cases = 10 months

3 Pure subaortic or aortic stenosis which exerts a considerable strain on the left ventricle Maximum age = 58 years mean age in 23 cases = 13 years

4 Pure mitral stenosis very rare Maximum age = 27 years mean age in 6 cases = 5½ years

5 Pure coarctation of the aorta of infantile type maximum age = 9 months mean age in 9 cases = 1¾ months

II *Cases of Arteriovenous Shunt with Possible Terminal or Transient Reversal of Flow (Cyanose Tardive)* In these cases arterial blood ordinarily enters the pulmonary circulation while venous blood rarely enters the systemic circulation Potentially cyanotic group

1 Patent ductus arteriosus Maximum age = 66 years mean age in 92 cases = 24 years

2 *Localized defects of aortic septum (communication between* base of aorta and pulmonary artery or base of right ventricle) Maximum age = 48 years mean age in 10 cases = 14 years

3 Localized defects of the interatrial septum including widely patent foramen ovale persistent ostium primum and persistent ostium secundum Maximum age = 70 years mean age in 68 cases = 27 years

4 Localized defects of the interventricular septum Maladie de Roger (Roger 1879) Maximum age = 49 years mean age in 50 cases = 14½ years

III *Cases of Venoarterial Shunt (Morbus caeruleus) (Maladie bleue)* Here venous blood in considerable quantity enters the systemic circulation Cyanotic group

A. Slight to moderate cyanosis

1 Defect of interventricular septum with dextroposition of the aorta Maximum age = 48 years mean age in 7 cases = 25 years

2 Cor triloculare biatriatum. Maximum age = 35 years mean age in 13 cases = $7\frac{1}{4}$ years

3 Pulmonary stenosis with patent foramen ovale Maximum age = 57 years mean age in 16 cases = 18 years

4 Tricuspid stenosis Maximum age = 28 years mean age in 3 cases = 15 years

5 Tricuspid atresia (imperforation from α privative not and τρῆσις perforation) with septal defects Maximum age = 56 years mean age in 16 cases = 5 [illegible] years

B Moderate to marked cyanosis

1 Pulmonary stenosis with defect of ventricular septum and dextroposition of aorta (tetralogy of Fallot 1888 the fourth element of the tetralogy being right ventricular hypertrophy) Maximum age = 59 years 8 months mean age in 85 cases = 12 years

2 Pulmonary atresia with defect of ventricular septum and dextroposition of the aorta Maximum age = 30 years mean age in 30 cases = 5 years

3 Transposition of arterial trunks with defect of ventricular septum Maximum age = 16 years mean age in 17 cases = 2 [illegible] years

C Extreme cyanosis

1 Cor biloculare with transposition of arterial trunks Maximum age = 16 years mean age in 2 cases = 9 years

2 Persistent truncus arteriosus (complete defect of aortic septum) with localized defect of interventricular septum Maximum age = 25 years mean age in 21 cases = 4 years

3 Cor biloculare with persistent truncus arteriosus (complete defect of cardiac and arterial septa) Maximum age = 14 days mean age in 5 cases = $6\frac{1}{2}$ days

4 Complete transposition of arterial trunks without defect of ventricular septum but with interatrial septal defect or patency of the ductus arteriosus Maximum age = 11 years mean age in 32 cases = 6 months

5 Pulmonary atresia with closed ventricular septum defective atrial septum and patent ductus arteriosus Maximum age = 20 years mean age in 10 cases = $1\frac{1}{4}$ years

6 Mitral atresia with aortic aplasia (lack of development from α privative not and πλάσσειν to form) defect of atrial and ventricular septa and patent ductus arteriosus Maximum age = 3/ years mean age in 5 cases = 10 months

7 Aortic atresia transposition of arterial trunks closed ventricular septum patent ductus arteriosus Maximum age = 15 weeks mean age in 12 cases = 2 months

A practical clinical classification which the author has recently found very helpful is presented in Table 5

Symptoms Congenital heart disease may be present without any symptoms whatsoever if there is no venoarterial shunt or especial strain on the heart such is commonly the case when there is but a slight to moderate degree of

Table 5

DIAGNOSABLE CONGENITAL DEFECTS OF HEART AND GREAT VESSELS—1960

			DEFECT	SYMPTOMS	SIGNS
I INTRACARDIAC	A NONCYANOTIC	a) WITHOUT A SHUNT	1 AORTIC OR SUBAORTIC STENOSIS	O	G d 5 rtl sub rtl y t lic murmur a d th ill
			2 PULMONARY STENOSIS	O	C de 5 p lm n y y t lic murm d thrill
		b) WITH A SHUNT	3 ATRIAL SEPTAL DEFECT	Slight t m der t h l dy p ea	Grad 2 t 3 p lm nary y t ll murm r P ++
			4 VENTRICULAR SEPTAL DEFECT	ith m ll defect dysp a ith larg es	Grad 5 s st lic m mu d th ill l f ternal bo der 4th pace
	B CYANOTIC		5 TETRALOGY OF FALLOT	Ret d d g wth Easily e h ust d I p a Sy p l tenden y	Cy l d fl g l bbi Gr d t 4 p lm ry y t ll murm
			6 PULMONARY STENOSIS +ATRIAL SEPTAL DEFECT	Slight t moderat he ic dy p ea	Cy l d fl er cl bbi g d l pi g i l ll lh od (d 4 t 5 p lm ry y t ll murmur d thrill
			7 EISENMENGER COMPLEX	S m as f 5 d hem pty is	Cy osl a d l bbi g M y b murm
			8 TRICUSPID ATRESIA	S m as f 5	S me as f
			9 TRANSPOSITION OF THE GREAT VESSELS	S me as f 5	Deep cy osis d l bbi g V y larg h rt Heart f il
			10 TAUSSIG-BING SYNDROME	Same as f 5	S me as for 7
II EXTRACARDIAC (Noncyanotic)			11 COARCTATION OF AORTA	O	Hypertensi in m d hyput i l lower I creased i ter ost l p l A rti ti us murm al g pi
			12 PATENT DUCTUS ARTERIOSUS	O	C ti u pulm ary m rm ften f il p ls pressur
			13 VASCULAR RING	Dy ph gia F eq t p lm ry i fecti	O

C ngenital heart block and cor nary omalies (both rry ar) m y b diagnosabl by lectrocardiogr m
*Tr nsposition f rt a d p rtial erridi g f tricul r sept l d fect by th large pulmonary artery arisi g primarily from th right entri le.

Table 5—Continued

DIAGNOSABLE CONGENITAL DEFECTS OF HEART AND GREAT VESSELS—1950

X RAY	ECG	BLOOD	CARDIAC CATHETERIZATION	SURGICAL RELIEF
Normal	Normal or Left ventricular hypertrophy	Normal	Normal	O
Pulmonary artery bump [illegible] enlarged pulmonary vascular markings usually decreased	Right ventricular hypertrophy + +	Normal	Pulmonary [illegible] pressure [illegible] than pressure [illegible] right ventricle	[illegible] valvulotomy
Very large pulmonary artery and lung hiluses. Heart slightly enlarged	R V H + +	Normal	Increased oxygen in right atrium. Increased pulmonary artery pressure	Beginning
Normal as [illegible] lary defects [illegible] heart may be enlarged	Usually Normal	Normal	Increased [illegible] right [illegible]	Beginning
Coeur en sabot with pulmonary ar[illegible] d[illegible] sometimes [illegible] decreased with [illegible] teral [illegible] circulation rarely increased	R V H + +	Polycythemia and increased hemoglobin	Catheter [illegible] pulmonary [illegible] easily enters aorta. Decreased pulmonary blood pressure	Partial correct (Blalock [illegible])
Much as in the case of the tetralogy of Fallot (see bo[illegible])	R V H + +	Polycythemia and increased hemoglobin	The [illegible] defect may be [illegible] by catheter. [illegible] between right ventricle and aorta as in the Tetralogy of Fallot [illegible] pulmonary ostium	Probably valvulotomy
Normal or prominent pulmonary ar[illegible] d right ventricle	R V H +	Same as [illegible] 5	Catheter enters either aorta [illegible] pulmonary artery. Increased pulmonary pressure	O
Small right ventricle and pulmonary artery	L V H	Same as [illegible] 5 and 6	Catheter enters left atrium [illegible] ter right ventricle	Partial correct (Blalock [illegible])
Both ventricles [illegible] enlarged. [illegible] narrow [illegible] low and wide in left [illegible]	R V H Usually	Same as [illegible] 5	Catheter enters [illegible] from right ventricle	Ortrial (Blalock + [illegible] septal-defect)
Large right ventricle [illegible] pulsating pulmonary arteries	R V H +	Same as [illegible] 5	Catheter enters aorta from right [illegible] pulmonary artery also	Ortrial (Blalock + [illegible] septal defect)
Small aortic k[illegible] Ribs notched	Normal hypertensive pattern	Normal	Normal	+
[illegible] pulmonary	Normal	Normal	Increased [illegible] pulmonary artery [illegible] pulmonary pressure ±	+
[illegible] esophagus and trachea [illegible] right aortic arch	Normal	Normal	Normal	+

uncomplicated patency of the ductus arteriosus coarctation of the aorta, or pure interventricular or interatrial septal defect On the other hand there may be marked symptoms if serious congenital cardiovascular lesions are present especially those attended by marked or extreme cyanosis (Groups III B and III C of Abbott s classification) and those with primary congenital hypertrophy marked coarctation of the aorta or pure stenosis of any of the valves

The symptom most commonly found is dyspnea particularly on exertion This dyspnea is of all grades occurring in the case of atrial septal defects as the result of overloading the pulmonary circulation and thus leaving too little room in the lungs for air and in the morbus caeruleus in paroxysms due probably to temporary increase of the amount of venous blood shunted into the systemic circulation which leads in turn to the appearance or increase of cyanosis Often there is but little dyspnea hardly noticeable which may show itself simply as an increase in respiratory rate Dyspnea was noted in 320 of Abbott s series of 1 000 cases of congenital heart disease

An interesting symptom doubtless related to both dyspnea and weakness is the frequent squatting during short walks or other exercise characteristic of children with the morbus caeruleus commonly the tetralogy of Fallot

Along with the higher grades of dyspnea cough is common hemoptysis is rare but may occur if there is pulmonary vascular engorgement from obstruction polycythemic congestion or heart failure Polycythemia may also give rise on occasion to epistaxis

Next in frequency after the respiratory and pulmonary symptoms are those of cerebral nature due chiefly to anoxemia but in the case of considerable polycythemia they are also due to the sluggish circulation and to cerebral thrombosis Weakness faintness headache dizziness syncope convulsions and coma delirium mania and transient or persistent paralyses have all been noted particularly in the cyanotic group of cases with congenital heart disease The greater the degree of cyanosis the greater is the likelihood of such cerebral seizures The cerebral manifestations may last from a few seconds to days at a time they often mean that the patient has been overtaxing his reserve In some cases they recur at intervals of a few days weeks or months for many years Not rarely they are the cause of death in the cyanotic cases Paradoxical cerebral embolism in cases with septal defects is responsible on occasion for abscesses of the brain

Gastrointestinal symptoms in congenital heart disease are not important except for the dysphagia caused by some anomalies of the aorta and its branches especially a right aortic arch Faulty circulation to the abdominal viscera may occasion anorexia nausea vomiting hematemesis tympanites constipation and combinations labeled biliousness If congestive failure supervenes an increase of such symptoms is common due especially to engorgement of the liver

Other symptoms are infrequent except for the complaint of coldness of hands and feet with cyanosis tingling in the extremities and abnormal susceptibility to infections especially of respiratory nature Palpitation is some

times complained of it is rarely severe Pain is very rare compared to dyspnea

Signs Often there are no signs of congenital heart defects outside of the heart and sometimes there are none even in the heart itself

Of all general signs only one is both common and important and that is cyanosis found in slight to marked degree in less than half of the cases of congenital heart disease (noted in 475 cases of Abbott s series of 1 000 doubtless an exaggerated proportion because cyanotic cases attract much more attention than noncyanotic) It may be terminal only due either to a reversal of flow between the sides of the heart through a shunt or to congestive failure or to both it was terminal in 124 of Abbott s series of 475 cyanotic cases It is particularly likely to be delayed in appearing after birth but it may become very intense in late childhood and in adult life giving rise to the terms morbus caeruleus and maladie bleue (blue disease) In Chapter 4 cyanosis has already been discussed here it need only be reiterated that it is dependent on three factors (1) the shunt of venous blood into the systemic circulation which shunt must be about 30 per cent of the total to pass the threshold for cyanosis (2) the dilatation of skin and mucous membrane capillaries with peripheral slowing of the blood stream and (3) insufficient oxygenation of the blood in the lungs The first two of these three factors are commonly present in the cyanotic group of cases of congenital heart disease and sometimes the third factor is also added if there is engorgement of pulmonary blood vessels such as occurs in cases of atrial septal defects with overloading of the lesser circulation or if there is pulmonary arterial and arteriolar sclerosis due to pulmonary hyperemia or hypertension or with increased viscosity of the blood in polycythemia, or in the rare cases of failure of the left ventricle and of congenital mitral stenosis A blueness of the eye grounds cyanosis retinae may be a relatively early sign of the morbus caeruleus

The next most characteristic and constant sign in the severe cases that is in those with well-marked and chronic cyanosis is clubbing of the fingers and toes (Figure 63) This was noted in 132 of Abbott s series of 1 000 cases It varies greatly in degree as does cyanosis and like cyanosis is not frequent in the youngest infants or children it develops later than cyanosis

Malnutrition and faulty development are not necessary accompaniments of congenital heart disease even of the severer types but they have frequently been found. In Abbott s series delayed development was noted 150 times Faulty cerebral growth mental retardation and Mongolian idiocy have been occasionally associated with congenital heart disease Arachnodactyly consisting of spider like fingers (and toes) and elongation of the entire body is seen in rare cases of congenital heart disease and hardly if ever occurs without cardiovascular defects mostly atrial septal and aortic wall defects

Edema of lungs and of legs ascites and congestion of the liver occur in congenital heart disease only if congestive failure supervenes

Cardiac examination Physical examination of the heart yields signs dependent on the type and degree of the congenital defects There may be little or no evidence of trouble in the heart even in some of the cases with such

serious lesions as the tetralogy of Fallot (pulmonary stenosis ventricular septal defect dextroposition of the aorta and big right ventricle) (Figure 64) There usually is but little enlargement in some cases however the apex impulse and the left border of dullness are well beyond the midclavicular line more increased transversely in the fifth intercostal space than downward in the sixth or seventh spaces since the right ventricle is enlarged more often than the left in congenital heart disease (Figure 71 opposite page 318) There may be increase in dullness to the right of the sternum usually there is not unless the heart shows well marked general enlargement or an abnormal position (dextrocardia) The region of the great vessels shows no abnormal dullness except with a patent ductus arteriosus or an atrial septal defect when the pulmonary artery may show itself to be enlarged by percussion in the

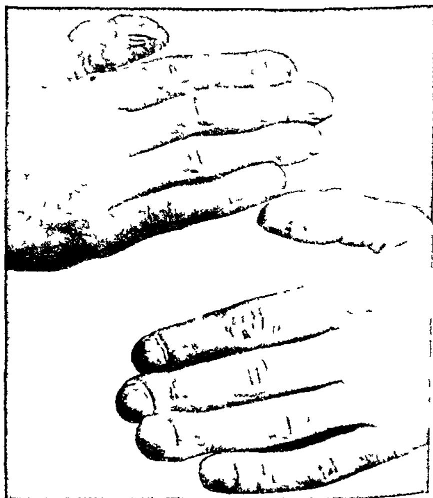
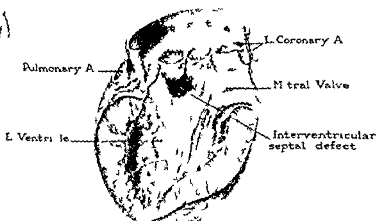


FIG 63 Photograph showing clubbing of the fingers in the morbus caeruleus (maladie bleue)

second and third intercostal spaces at the left of the sternum Palpation usually reveals a more or less normal apex impulse Occasionally there is felt a systolic thrill located at the left border of the sternum midway between upper and lower ends if there is a pure interventricular septal defect somewhat higher if there is pulmonary or infundibular stenosis and maximally in the second right intercostal space if there is congenital subaortic or aortic stenosis There often is a continuous thrill at the left border of the upper sternum in cases of patent ductus arteriosus

Auscultation may reveal no abnormalities even with serious congenital



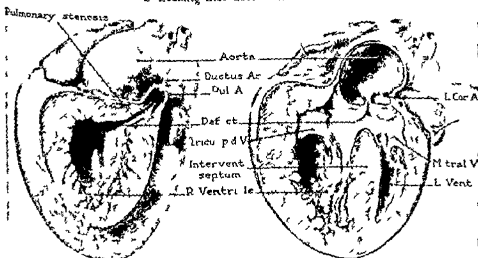


FIG 64 Photograph of congenital heart showing very large right ventricle in tetralogy of Fallot (Kindness of Dr Helen Taussig Johns Hopkins Hospital Baltimore and The Commonwealth Fund New York City)

defects There may or may not be murmurs When murmurs occur they are as a rule systolic in time and loudest just to the left of the sternum where they may be very limited in extent, located in the first intercostal space in some cases of patency of the ductus arteriosus, in the second space with pulmonary stenosis in the third space with infundibular stenosis and in the third and fourth interspaces in most cases of interventricular septal defect (Roger s murmur) Diastolic murmurs are uncommon as solitary findings they have been noted where the pulmonary or aortic valve has been defective and in rare cases of patency of the ductus arteriosus or larger interatrial septal defects They may also accompany the systolic murmurs of dilated pulmonary arteries in cases of large atrial septal defects when they are the result of a stretching of the pulmonary valve rings—such murmurs are likely to be transient like the Graham Steell murmur A continuous murmur roaring and machine like in character extending throughout systole and diastole with systolic accentuation is not infrequently found in the first three intercostal spaces just to the left of the sternum maximal in the first space When present it is usually pathognomonic of patency of the ductus arteriosus if venous hums transmitted from the neck and very rare and obvious arteriovenous aneurysms of the great vessels are excluded such exclusion is easily accomplished

It is important to remember that murmurs and thrills are very variable accompaniments of congenital heart defects the larger the defect the less likely are murmurs and thrills to be found A narrow caliber of patent ductus arteriosus or of interventricular septal defect is much more likely to give rise to murmur and thrill than is a large and much more serious patency which may show no murmur or thrill at all In the case of a stenotic lesion like pulmonary stenosis or coarctation of the aorta the greater the degree of stenosis the more frequently are murmur and thrill to be found but here too when the defect is extreme and there is complete atresia murmur and thrill will be absent One must use much judgment therefore in the analysis of the findings on physical examination of the heart in congenital cardiac disease it is necessary to depend more on other methods of examination

Heart sounds rate and rhythm are generally not abnormal in cases with congenital cardiovascular defects except in the case of pulmonary stenosis when the second sound in the second left interspace tends to be much diminished while with ductus patency or atrial septal defect it is usually accentuated With failure the sounds may decrease and the rate may increase but marked disturbances are rare and arrhythmia is very uncommon Premature beats and paroxysmal tachycardia are seen infrequently Atrial fibrillation is very unusual There is one disturbance of rhythm however which is an important though rare accompaniment of congenital heart disease this is *heart block* A few cases of unquestionable congenital heart block are on record The block may be either partial or complete It has been thought to be associated with interventricular septal defect and in three cases with postmortem study this defect was found to be extensive in degree (Wilson and Grant 1926 Yater 1928 and personal communication Abbott 1930)

Blood pressure The systolic blood pressure in congenital heart disease is not remarkable It tends to be low especially where there is an atrial septal defect or subaortic (or aortic) stenosis or much polycythemia and peripheral vasodilatation then the pulse pressure also is low An interesting finding of a fullness of pulse due to low diastolic pressure is to be noted in some cases of patency of the ductus arteriosus of extensive degree where a hydrodynamic situation exists somewhat comparable to that in the case of aortic regurgitation Also it is an important fact for diagnosis that with coarctation of the aorta the blood pressure (systolic and pulse pressure) in the upper extremities is higher than that in the lower extremities sometimes to a marked degree when the coarctation is extreme

Roentgenologic study Roentgen ray study of the heart and great vessels in congenital heart disease may be a great aid but it is sometimes of no help at all and serious cardiovascular defects may exist with no clear indication of their presence by roentgen ray Positive findings by this method of examination may be however the only clue to trouble either to its existence or to the particular lesion or lesions especially in differentiating left heart involvement from right and in revealing abnormalities of the great vessels Right ventricular enlargement may be revealed more by the so-called *coeur en sabot* or wooden shoe shape of heart shadow than by any increase in size of the cardiac silhouette (Figure 72 page 319) this is found especially when the pulmonary artery is hypoplastic (small) as in the tetralogy of Fallot but not when it is large even though the right ventricle is very big as with an atrial septal defect Marked enlargement of the whole heart shadow is characteristic of congenital idiopathic hypertrophy of coronary anomalies (the left arising from the pulmonary artery) and of von Gierke s glycogen storage disease (see page 323) Undue prominence of the shadow of the pulmonary artery may confirm the diagnosis of patent ductus arteriosus (see Figure 80 page 339) When there is no characteristic murmur of patency of the ductus arteriosus bulging of the pulmonary arc as seen by roentgen ray strongly favors the diagnosis of a defect in the septum between the atria and the larger the bulge the more likely is the latter defect Errors have frequently arisen in the past from relying on roentgenologic rather than on auscultatory evidence of ductus arteriosus patency Marked dilatation of the vessels in the lung hilus shadows helps to establish the diagnosis of an interatrial septal defect (see Figure 68 page 313)

Increase in the shadow of the ascending aorta is especially the rule in the tetralogy of Fallot where the aorta is both dextroposed and abnormally capacious it may also be found to a lesser degree with coarctation of the aorta Decrease in the ascending aortic shadow is common in the case of atrial septal defects and with aortic stenosis Absence of the aortic arch shadow may be found if there is considerable coarctation of the aorta or a right sided arch may be visible The esophagus and trachea may be displaced forward by a right sided aortic arch and compressed by a vascular ring And finally notching of the ribs may be evident due to dilated intercostal arteries in cases of coarctation of the aorta (see Figure 77 page 332)

Electrocardiographic examination In some cases of congenital heart disease the electrocardiogram is normal or so slightly divergent from the normal that it is in no way helpful Even negative findings are useful however since they tend to rule out right sided lesions when there is uncomplicated defect of the interventricular septum patency of the ductus arteriosus or coarctation of the aorta There are three conditions where the electrocardiogram is especially helpful and shows characteristic changes The more common of these three is right ventricular enlargement, usually associated either with pulmonary stenosis most commonly found in that combination of defects already described as the tetralogy of Fallot or with interatrial septal defect These conditions give rise to right ventricular preponderance often of marked degree In fact the greatest degree of right ventricular preponderance known is found in congenital heart disease With this abnormal right axis deviation there is found usually an abnormal increase of amplitude of the *P* (atrial) wave The second characteristic electrocardiographic pattern is that showing abnormal left axis deviation due to enlargement of the left ventricle in the rare cases of tricuspid atresia here the electrocardiogram may be the chief clue in the differentiation from the tetralogy of Fallot since both conditions cause considerable cyanosis and finger clubbing The third characteristic electrocardiographic finding is in the case of mirror picture dextrocardia the so-called heterotaxy (ἕτερος opposite and τάξις arrangement) whether complete or isolated (that is with or without abdominal visceral transposition also), here Lead 1 of the electrocardiogram is completely inverted and Leads 2 and 3 are reversed (Figure 65) Isolated congenital dextrocardia as a matter of fact has not been found to occur without other more important congenital cardiovascular defects (Roesler 1930) It is of great importance to be certain that this electrocardiogram is caused by the position of the heart and not by artifact due to crossing of the first two lead connections If as occurs in some cases dextrocardia is associated with some defect which results in right ventricular enlargement then the electrocardiogram will indicate a marked degree of abnormal left axis deviation but with inverted *P* waves in Lead 1 In cases of the two-chambered heart (cor biloculare) or of the three chambered heart with one ventricle (cor triloculare biatriatum) there tend to be biphasic *QRS* waves of wide amplitude in all three classical limb leads and in the precordial leads Finally as noted above there are rare cases of congenital heart block either complete or partial requiring electrocardiography for confirmation it is of interest that the ventricular rate in cases of congenital complete heart block tends to be rather high in the fifties or sixties as a rule and so may obscure the disorder of rhythm until an electrocardiogram is obtained

Other data Urine Albuminuria is common in the severer types of congenital heart disease partly because of engorgement due to polycythemia less often because of slight to moderate congestion from cardiac insufficiency

The blood Unless there is cyanosis or infection the blood cell counts and hemoglobin will be normal With a complicating infection polymorphonuclear leukocytosis is of course expected With cyanosis and a shunt of venous blood

into the systemic circulation a polycythemia is found increasing in degree as the shunt and cyanosis increase A red blood cell count of 6 or 7 millions is common in cases classed as the morbus caeruleus and in extreme cases even 10 11 and 12 million erythrocytes have been reported Along with this increase of red cells there is an increase of hemoglobin which usually runs

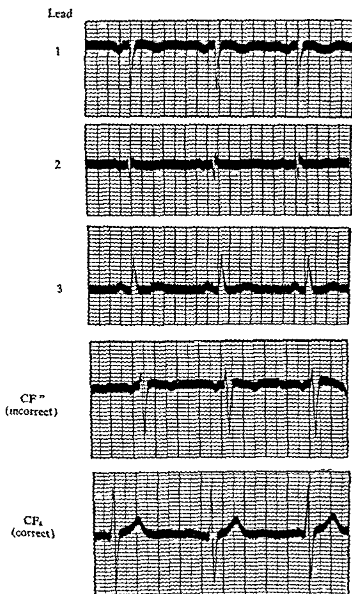


FIG. 65 Electrocardiogram (four leads) in a case of congenital dextrocardia with complete situs inversus and without other congenital defects The first Lead "CF" taken (labeled "incorrect" above) was erroneously obtained from the left side On discovery of the dextrocardia the correct Lead CF was taken as shown above J G male age 30

parallel, to 110 120 130, and in rare cases up to 180 or 200 per cent (25 gm) The reason for these increases is obvious Since the oxygen saturation of the hemoglobin is low because of lack of contact of a large percentage of the red cells with oxygen in the alveoli of the lungs an increase in the number of red cells occurs in order to transport sufficient oxygen to the tissues The oxygen capacity may almost double while the oxygen saturation of the blood is nearly halved the result is close to a normal amount of oxygen in the blood under favorable circumstances

The viscosity of the blood is much increased in polycythemia since viscosity is controlled chiefly by the number of cellular elements in the blood It may be increased several fold This means more work for the circulation and peripheral vasodilatation occurs in part to allow a more complete oxygen distribution to the tissues and in part to relieve the strain on the heart The actual blood volume is also increased in polycythemia the amount depending on the degree of cellular increase

The amount of oxygen and of carbon dioxide in the blood has already been referred to (Chapter 10) It is normal in cases of congenital defects without unusual communications but there are two abnormal situations dependent on the direction of the shunt venoarterial and arteriovenous

Venoarterial shunts An abnormally low oxygen saturation of the hemoglobin of the arterial blood is common in the case of the defects which result in venoarterial shunts it may reach even the low figure of 58 to 62 per cent (*Talbott et al 1941*) *If about one third of the venous blood entering the* right heart chambers is shunted directly into the systemic circulation the percentage of blue-colored reduced hemoglobin in the arterial blood may be increased to 20 per cent instead of the normal 1 to 5 per cent (or 4 volumes per cent instead of the normal ½ to 1 volume per cent) passing the threshold at which cyanosis appears A greater shunt than this yields still more reduced hemoglobin in the arterial blood and a greater degree of cyanosis in the case already referred to with very low oxygen saturation of the arterial blood it was estimated that 75 per cent of the blood in the heart chambers traversed the right to left shunt (Talbott et al 1941) However it is possible for a smaller shunt than that of one third to produce cyanosis provided there is an abnormally high red cell and hemoglobin content It is not the percentage but the total amount of reduced hemoglobin whether originating by shunt in heart or lungs or by peripheral stasis that is primarily responsible for the abnormal color of the blood made obvious by dilated capillary vessels If in the capillaries there are 5 gm or more of reduced hemoglobin per 100 cc of blood cyanosis will result With normal red cell and hemoglobin content 3 5 to 4 volumes of reduced hemoglobin in the arterial blood will yield 6 5 or more volumes per cent in the capillary blood (or 5 gm per 100 cc) With polycythemia and an *increased oxygen content capacity of the blood due to increased* hemoglobin the same amount of reduced hemoglobin may be present in the capillary blood to cause cyanosis even though the actual percentage of oxygen unsaturation of the arterial blood due to a smaller shunt may be only 10 or

15 per cent If it were possible for severe anemia and a very low hemoglobin content (and therefore a low oxygen capacity of the blood) to develop in cases of venoarterial heart shunts it might be impossible to reach the stage of cyanosis no matter how little the oxygen saturation of the arterial blood might be because as much as 5 gm of reduced hemoglobin could not be produced in 100 cc of capillary blood The occurrence of severe anemia in the morbus caeruleus is however not likely since it would seem to be incompatible with life

Two other factors often enter into congenital heart disease with a venoarterial shunt to decrease the oxygen content of the capillary blood One of these is the structural and functional state of the lungs a factor which even with cardiac catheterization makes difficult any accurate estimation of the amount of the shunt Polycythemia and thickening of the alveolar capillaries are inevitable accompaniments of advanced morbus caeruleus Failure of proper oxygenation of the blood in the lungs may add its effect to that of a venoarterial shunt in reducing the oxygen content of arterial and capillary blood and in causing cyanosis The second additional factor consists of the slowing of the peripheral circulation which decreases still further the oxygen content of capillary blood in the morbus caeruleus The content of oxygen in the venous blood follows that of the arterial blood in such cases but is several volumes per cent lower An interesting and important factor that helps to decrease the oxygen unsaturation of the blood in cases of right to left shunt is the development of a somewhat compensatory collateral bronchial circulation The bronchial arteries and their branches course along the bronchi and bronchioles parallel to the pulmonary arteries but with a much more tortuous course They may become considerably enlarged in cases of the morbus caeruleus particularly the tetralogy of Fallot and thus may bring a good deal of blood to the lungs for oxygenation This bronchial circulation may appear quite clearly in the x ray pictures of the chest even though the pulmonary artery and its branches are much diminished in such shadows

The carbon dioxide content of the arterial and venous blood in the morbus caeruleus tends to be low rather than high (as one might at first have expected it to be) This is probably due to increased ventilation whereby the carbon dioxide which is thirty times more diffusible than oxygen is pumped out of the blood in the lungs and also to a tissue acidosis from faulty metabolism (due to the poor circulatory state) with retention of bicarbonate in the tissues

An interesting effect of venoarterial shunts on tests of the rate of the circulation (see Chapter 10) is worthy of note In cases with such shunts in the absence of heart failure not only is arm vein to tongue arterioles time much reduced below the usual normal because of cutting out the lesser circulation from a good deal of the blood flow but the total round trip (arm to tongue or arm vein to leg artery) time may actually be or seem to be slightly faster than the arm to lung time as in tests with ether

Arteriovenous shunts The other particular influence of congenital cardiac defects on the blood gases is in the case of arteriovenous shunts particularly

atrial septal defects patency of the ductus arteriosus and interventricular septal defects If large enough these defects cause by their admixture of arterial with venous blood abnormally high oxygen and abnormally low carbon dioxide content of the venous blood entering the pulmonary circulation (Burwell Eppinger and Gross 1940 and 1941)

Cardiac catheterization Catheterization of the heart chambers and pulmonary artery has been discussed in Chapter 10 but one should add here that perhaps its most useful application is in the diagnosis of congenital defects a higher blood content of oxygen than normal is found in the right atrium in the case of an atrial septal defect in the right ventricle in the case of a ventricular septal defect and in the pulmonary artery in the presence of a patent ductus arteriosus Moreover, the catheter can be passed under fluoroscopy through an atrial septal opening into the left atrium or into the aorta in the tetralogy of Fallot (see Figure 56 pages 228 and 229)

Course and prognosis The course and prognosis of congenital heart disease vary with the type In cases with relatively unimportant lesions where there are no shunts for example abnormal chordae tendineae and valve cusps simple dextrocardia pericardial anomalies slight to moderate coarctation of the aorta and in cases with lesser degrees of arteriovenous shunt through uncomplicated patent ductus arteriosus or interventricular septal defect life may not be handicapped or shortened and with all these conditions old age has been comfortably reached with no cardiac disability due to these defects Even these lesions are however somewhat perilous because of the possibility of their being the site of bacterial infection especially of streptococcal nature This infectious invasion serious and in former days so often fatal is not rare particularly in the case of bicuspid aortic valves of ventricular septal defects and of patent ductus arteriosus in Maude Abbott s series 9 of 32 cases (28 per cent) of the first named 13 of 50 cases (26 per cent) of the second and 21 of 92 cases (23 per cent) of the last named developed subacute bacterial endocarditis or endarteritis Gelfman and Levine (1942) found the incidence of acute and subacute bacterial invasion in patients over the age of two years with the more common congenital cardiovascular defects as follows ventricular septal defects (Roger s disease) 57 1 per cent of 14 cases patent ductus arteriosus 28 6 per cent of 14 cases pulmonic stenosis 29 4 per cent of 17 cases bicuspid aortic valves 21 2 per cent of 52 cases tetralogy of Fallot 28 6 per cent of 7 cases coarctation of the aorta 10 per cent of 10 cases and *atrial septal defects none among 45 cases*

In the case of the more serious defects the course is difficult and the prognosis grave Both the difficulty of the course and the seriousness of the prognosis depend on two factors The first of these factors is the degree of anoxemia which is indicated to a certain extent by the degree of cyanosis This anoxemia affects all organs of the body especially the brain and the heart The second factor is the amount of direct strain on the heart Two other points are to be remembered Cyanosis does not usually appear early in infancy and yet the prognosis at this early age may be bad Moreover, anoxemia

and cyanosis are not strictly comparable since there may be a sufficient quantity of oxygen in the blood for the tissues if there is a polycythemia and yet there may be also enough reduced hemoglobin to cause cyanosis This explains why many cyanotic individuals are not dyspneic

The most serious lesions like ectopia cordis abdominalis uncomplicated transposition of the great vessels the two chambered heart and pulmonary or aortic atresia with closed ventricular septum may be so crippling that a miserable existence is possible for but a few days weeks or months at best

Sudden unexpected death is not a rare termination in the case of infants and children with congenital heart disease even in those who show little or no evidence of the condition during life (Levinson 1941)

The less grave cases of the morbus caeruleus may occasionally survive to adult life or even into middle age if they live carefully and are fortunate enough to escape serious complications Some striking cases are on record of long survival especially one of a noted musician who lived a useful life to the age of 59 years and 8 months in spite of the tetralogy of Fallot and another of a woman with marked pulmonary valve stenosis and atrial septal defect who lived actively until she died of right heart failure at the age of 74 years and 11 months Both diagnoses were confirmed by postmortem examination and both patients showed cyanosis and clubbing of the fingers from early childhood (White and Sprague 1929 White Hurst and Fennel 1950) Limitation of activity is almost always enforced by the morbus caeruleus because of dyspnea weakness and cerebral symptoms

Complications The chief complications of congenital heart disease are infections especially pneumonia cerebral attacks—syncope coma convulsions and hemiplegia due to thrombosis or hemorrhage—bacterial endocarditis or endarteritis and congestive heart failure These complications are often fatal An analysis of 453 autopsied cases of all ages of congenital heart disease in Boston hospitals gave a total incidence of 6 6 per cent affected by subacute bacterial endocarditis or endarteritis as compared with 16 6 per cent among those over the age of 2 years (Gelfman and Levine 1942) This dread disease is now fortunately in major part preventable or curable because of the advance in surgical therapy and of the introduction of penicillin An uncommon complication in cases with septal defects is cerebral infarction or abscess from paradoxical embolism

Treatment In the first two editions of this book (1931 and 1937) it was stated that there is no curative treatment surgical or medical for congenital cardiac defects but notable advances have been made in the last twelve years in several particulars (1) patency of the ductus arteriosus is now curable by surgery (2) coarctation of the aorta can also be corrected surgically in nearly all young cases (3) a vascular ring constricting trachea and esophagus can be broken (4) certain instances of the morbus caeruleus in particular the tetralogy of Fallot can be greatly helped by surgery and (5) penicillin can cure many of the cases infected by the alpha hemolytic streptococcus And other advances are in the offing

In some cases of congenital heart disease no special care is needed though even the least serious case should be protected against infection to avoid complicating bacterial invasion and pneumonia Since the teeth and gums harbor in particular the alpha hemolytic streptococcus the cause of subacute bacterial endocarditis and endarteritis in the vast majority of cases it is wise to protect by penicillin the patients with congenital cardiovascular defects who are to be subjected to dental extractions or other extensive treatment 300 000 units should be given intramuscularly 1 hour before the dental treatment and again 3 hours after

Tonsillectomy is probably advisable in childhood though not in infancy provided the tonsils are diseased and provided there is not too great a risk for operation Protection from fatigue and care to provide suitable diet are to be urged for the cyanotic cases and for those with much heart strain Finally complications of congestive failure cerebral lesions and infections are to be treated as such by rest in bed digitalis as required penicillin and other measures If the victim of congenital heart disease is well protected his life may sometimes be prolonged for many years

Differential diagnosis Congenital heart disease may resemble two other conditions acquired heart disease and pulmonary disease It is to be differentiated from the former by the history of involvement of the heart from birth if that is reliably obtained and by the characteristic signs—certain murmurs heart shape cyanosis clubbing of the fingers and typical electrocardiograms when such exist (as described above), in a few instances the differentiation is very difficult Acquired heart disease especially rheumatic subacute bacterial and coronary may be superimposed on congenital cardiovascular defects

It is more difficult to differentiate pulmonary disease such as pulmonary fibrosis with emphysema or pulmonary endarteritis when it is attended by cyanosis polycythemia and clubbing of the fingers from the morbus caeruleus of congenital heart disease especially if the latter happens not to show characteristic murmurs electrocardiograms or orthodiagrams Great care must be taken in analyzing such cases

The discovery of congenital anomalies elsewhere in the body favors somewhat the diagnosis of congenital cardiovascular defects when the differentiation of the type of heart disease is difficult or obscure

The more common individual congenital cardiovascular defects should in the present day and age (in striking contrast to a generation ago) usually be differentiated with ease except in infancy It seems likely that the ratio of diagnosability of individual defects during infancy to that after infancy is about 30 per cent as compared to 90 per cent Rare defects are however as a rule undiagnosable

INDIVIDUAL CONGENITAL CARDIOVASCULAR DEFECTS

It has become possible during the present generation clinically to recognize the majority of congenital cardiovascular defects and therefore they have

assumed an increasing importance in the practice of medicine They will be presented in the following order congenital malposition of the heart con genital abnormalities of the cardiac chambers and septal defects congenital myocardial disease congenital endocarditis and valvular defects congenital pericardial defects congenital anomalies of the great arteries and veins and congenital anomalies of the coronary arteries

CONGENITAL MALPOSITION

Congenital malposition of the heart includes dextrocardia and ectopia cordis

Congenital dextrocardia is of two main types occurring with about equal frequency (1) In the first type without transposition the heart is slightly rotated and rests in the right side of the chest The left chambers lie to the left and anteriorly the right chambers lie to the right and posteriorly and the apex is made up either of the right ventricle or of the right side of the common ventricle Almost invariably in this type there is some serious associated congenital anomaly like a single ventricle The prognosis and course of the congenital heart disease depend on these associated anomalies and not on the dextrocardia (2) The other variety of congenital dextrocardia is that attended by transposition of the chambers whereby the left chambers lie on the right side and form the right border and apex and the right chambers lie on the left side Almost invariably the abdominal viscera are also trans posed (complete heterotaxy or situs inversus) With this type of congenital dextrocardia that is the mirror type there are usually no other congenital cardiac defects at least of serious nature unless the dextrocardia is isolated that is occurring without associated general transposition of other organs (Roesler 1930) Dextrocardia uncomplicated by other cardiovascular defects is unimportant clinically It is discovered accidentally on routine physical or roentgen ray examination or even by electrocardiography and in no way affects activity or duration of life A pathognomonic sign of this mirror type of congenital dextrocardia is electrocardiographic complete inversion of Leads 1 and aVR and transposition of Leads 2 and 3 aVL and aVF and of the precordial leads (Figure 65) An interesting complication of the situs inversus which may in some cases be regarded as a stigma of an associated congenital maldevelopment is bronchiectasis which was found in 5 of the 23 cases of the situs inversus (21 7 per cent) recorded at the Massachusetts General Hospital in the fifty years from 1886 to 1936 while of the general hospital population over that period of time bronchiectasis was diagnosed in but 0 3 per cent (Churchill and Adams 1937)

Ectopia cordis a very rare defect consists of the malposition of the heart outside of the thoracic cage either in the abdomen or actually projecting out side the body wall It is of academic interest only since attempts at surgical correction have as yet been unsuccessful and life is almost invariably very brief a matter of a few days or at best a few weeks

CONGENITAL ABNORMALITIES OF CARDIAC CHAMBERS SEPTAL DEFECTS

Congenital abnormalities of the cardiac chambers include complete and partial absence of atrial and ventricular septa These defects may be unimportant discovered only at postmortem examination after a long and active life and unsuspected before death or they may be of great importance permitting only a few hours or days of existence after birth The degree of the defect and complicating abnormalities determine the importance of each lesion

Atrial Septal Defects

Atrial septal defects are much more numerous than any other anomaly in congenital cardiovascular disease In Abbott s series of 1 000 cases there were 402 individuals with openings between the atria which included true (not slit like) patency of the foramen ovale (290 cases) persistent ostium primum in the lower part of the septum (36 cases) persistent ostium secundum in the upper part (19 cases) multiple defects (28 cases) and complete *absence of the septum in the biloculate heart (14 cases) or in the triloculate* heart with one atrium and two ventricles (15 cases)

Patency of the foramen ovale is of the least importance and greatest frequency of all congenital cardiac abnormalities The foramen ovale is a valve like opening between the atria developing from the ostium secundum of the embryo and functioning in fetal life to allow the passage of considerable blood directly from venous to arterial circulation without going through the lungs It closes soon after birth and usually becomes sealed within the first three months of life In many cases it remains anatomically slightly patent as a valve slit but as such it is functionally inactive When the slit opening is small the patent foramen ovale is of absolutely no importance but if it is moderately large and the right atrial pressure is much raised venous blood may pass into the left atrium and even occasion slight cyanosis Clinically unimportant patency of the foramen ovale has been reported in nearly one quarter of all autopsied cases (with a range from about one eighth to one third)

In a few cases the foramen ovale remains really patent and in such cases it may prove to be of some importance In one series of 500 hearts (250 from white and 250 from Negro subjects) probe patency of the foramen ovale was found in 85 cases (17 per cent) while in only 2 cases (0 4 per cent) did the valvula foraminis ovalis actually fail completely to cover over the foramen ovale (Seib 1934) Wide patency is usually associated with and probably caused by other more important congenital abnormalities such as pulmonary stenosis or transposition of the great arterial trunks or with acquired mitral stenosis and these other defects determine the course and prognosis Of a

The terms "atrial septum" and "ventricular septum are used interchangeably with interatrial septum" and "interventricular septum" respectively

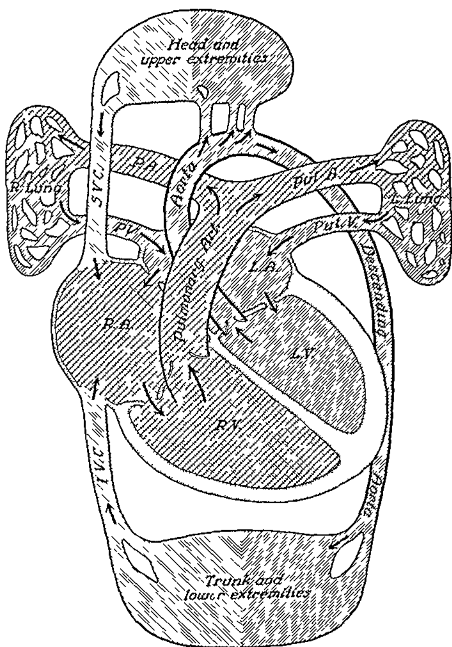


FIG 66 Diagram of atrial septal defect (Kindness of Dr Helen Taussig Johns Hopkins Hospital Baltimore and The Commonwealth Fund New York City)

series of 290 cases of patent foramen ovale (Abbott 1931) only 40 were instances of pure or primary patency

Atrial septal defects of importance are those that involve relatively large areas of the septum (1) The *primitive ostium primum* in the lower part of the septum (36 cases in Abbott s series of 1 000 individuals with congenital cardiovascular defects 18 of the 36 complicating other defects) or (2) the *primitive ostium secundum* (from which the foramen ovale develops) in the upper part of the septum (19 cases of Abbott s series 9 of which complicated other defects) or (3) *absence of the entire atrial septum* giving a three chambered or *triloculate heart* (*cor triloculare biventriculare*) if there are two ventricles or a two-chambered or *biloculate heart* (*cor biloculare*) if there is but one ventricle (15 cases of the former and 14 of the latter in Abbott s series) Females showed a slight preponderance (44 to 35) in these three categories of atrial septal defect in Abbott s series All these lesions are more serious than patency of the foramen ovale persist from an earlier stage of fetal life and are often complicated by other anomalies Persistence of the ostium primum is not only more common than that of the ostium secundum but it is also much more serious (Figure 66 opposite page 310)

The explanation of the increase in size and work of the right heart chambers in these cases is that extra blood often in large amount enters the right atrium from the left atrium through the septal defect this direction of flow has been assumed to be due to a slightly higher pressure in the left atrium but Uhley (1942) has shown that an important perhaps the most important cause of this direction of flow is the effect of gravity the right atrium being anatomically situated below the left, the septum lying more or less horizontally

In the cases of persistence of the primary and secondary ostia there may be no symptoms or signs and the subjects may live fairly long lives though not so long as those with foramen ovale patency Enlargement and failure of the right ventricle are however common Loud systolic murmurs rarely accompanied by thrills are found in most of the cases chiefly in the pulmonary valve area Years ago they were ascribed to the septal defect itself but it has become evident that they are due to the dilatation of the pulmonary artery which is secondary to the increased pulmonary circulation or to a complicating mitral valve defect With large atrial defects the electrocardiogram shows marked right axis deviation (Figure 67) and the roentgen ray shows enlargement of the right atrium right ventricle and pulmonary artery and its branches large and small and also hypoplastic aorta (Figure 68) it is probable that in some cases at least twice as much blood passes through the pulmonary circulation as through the systemic Paradoxical embolism may occur Cyanosis is infrequent but may appear as an occasional or terminal event when the right atrial pressure becomes greater than that in the left atrium or constantly if there is a complicating pulmonary stenosis

An analysis of 53 cases of atrial septal defects 10 with necropsy control (Bedford Papp and Parkinson 1941) showed a preponderance of females in the ratio of 4 to 1 the age of death mostly from 30 to 50 years and the

cause of death in the autopsied cases congestive heart failure in 3 pulmonary infarction in 2 embolism (one paradoxical) in 2 subacute bacterial endocarditis (a very rare complication) in only 1, bronchopneumonia in 1 and surgical operation in 1 the upper part of the septum was involved in 8 of these 10 cases A pulmonary systolic murmur was found in 32 of the entire series and an accentuated pulmonary second sound in 31, followed by a diastolic murmur (probably due to a stretching of the valve ring) in 10 Slight or late cyanosis was present in 31 cases Excessive pulsation of the lung hilum was noted by roentgen ray in 31 of the 50 cases so studied but a hilar dance was observed in only 5 Normal rhythm was the rule being present in 47 cases

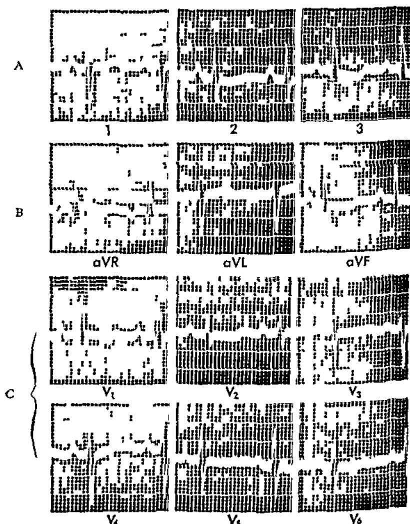


FIG 67 Electrocardiogram in a case of atrial septal defect female age 26 (A) Bipolar limb leads 1 2 and 3 (B) unipolar limb leads aVR aVL and aVF (C) six precordial leads V_1 to V inclusive Time = 0 04 and 0 20 second amplitude 1 mm = 0 10 mv

Right ventricular preponderance was present in the electrocardiogram in 41 cases and complete right bundle branch block in 5 others

When there is but one atrium life is generally much limited but some cases of remarkable longevity are on record with few symptoms or signs Cyanosis is the rule thrills and murmurs are infrequent and dyspnea is inconstant Of 5 cases with one atrium and two ventricles cited by Abbott one lived to the age of 31 years the mean duration of life was 6 years Of 9 cases with



FIG 68 Roentgenogram of thorax of case of congenital defect of the interatrial septum showing extreme degree of dilatation of the pulmonary artery and its branches right and left along with enlargement of the right ventricle Note the shadows of cross sections of arteries Small aorta (Kindness of Dr Hugo Roesler Temple University Philadelphia)

one atrium and one ventricle the oldest case was 16 years at death and the mean age was 3¼ years

A very interesting association is that of *mitral stenosis with a defect of the interatrial septum* (Abbott 1915 Lutembacher 1916) There is a combined effect of both lesions The left atrium tends to remain small and the right atrium becomes very large receiving as it does the extra blood from the left atrium as well as from the great veins There have been noted murmurs over the sternum or just to the left presystolic and systolic in time ascribed to the passage of blood through the septal defect but it is naturally difficult to differentiate such murmurs from those due to the mitral valve disease and

transmitted thither certainly the most common cause of the basal systolic murmur in such cases is dilatation of the pulmonary artery which is invariably present The congenital deficiency of the atrial septum has been given credit for relieving somewhat the burden imposed on the pulmonary circulation and right ventricle by marked mitral stenosis and thereby aiding the prolongation of life Remarkable cases of this combination of mitral stenosis and atrial septal defect are on record including that of a woman of 74 years of age who had passed successfully through eleven pregnancies and three abortions (Firket 1880) a woman of 61 years who had gone through seven pregnancies without heart failure (Lutembacher 1916) and two other cases aged 74 and 62 years respectively (Bonnabel 1906) However interatrial septal defects alone if large impose a serious burden on the right heart and pulmonary circulation and therefore it does not appear likely that they can aid much in relieving the heart or lungs in the presence of mitral stenosis except probably to prevent attacks of acute pulmonary edema which are an infrequent but distressing complication of tight mitral stenosis when the heart beats too rapidly

A large atrial septal defect is always to be suspected when there is the combination of a loud pulmonary systolic (not continuous) murmur, marked prominence of the pulmonary artery and lung hilus shadows and small aortic shadow by roentgen ray and pronounced right ventricular preponderance by electrocardiogram in a person in fairly good health save for a variable amount of dyspnea In differential diagnosis it may be said that the cor pulmonale due to pulmonary disease or endarteritis gives less right axis deviation and less lung hilus engorgement while mitral stenosis is of course attended by its characteristic diastolic murmur

Surgical correction of uncomplicated but important atrial septal defects is now on trial and has been successful in a few cases (Murray 1948)[3] Correction of the atrial septal defect was done by passing sutures through the anterior wall beginning to the right of the aorta and pulmonary artery to emerge posteriorly through an area between the superior vena cava and right pulmonary veins These sutures were tied together posteriorly drawn taut and tied down firmly thus compressing the anterior and posterior walls of the atria In one of the cases described the right atrium diminished to at least one half its size in two minutes the patient s condition was improved

Ventricular Septal Defects

Next in frequency after atrial septal defects come ventricular septal defects of which in Abbott s series there were 315 instances including localized openings isolated or complicated (274 cases) complete absence of the septum in the biloculate heart (14 cases) and in the triloculate heart with one ventricle and two atria (27 cases)

Localized ventricular septal defects are generally associated with other

[3] In March 1951 Murray (personal communication) stated that he had performed the operation of closure of an atrial septal defect in seven cases with considerable improvement in three some improvement in two and death in two

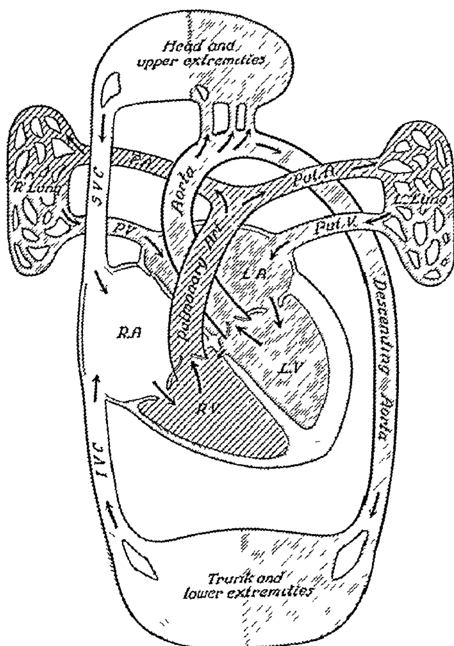


FIG 69 Diagram of ventricular septal defect (Kindness of Dr Helen Taussig Johns Hopkins Hospital Baltimore and The Commonwealth Fund New York City)

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congenital defects and are almost invariably found at the base of the heart just below the aortic valve in the region of the so-called undefended or fibrous space Of the series of 274 cases collected by Abbott the ventricular septal defects were in this basal position in all but 17 and these 257 basal defects complicated other abnormalities in 207 cases leaving 50 instances of the pure defect. Seven of the 207 complicated cases had but a right sided (dextro-) position (Rechtslage) of the aorta as an additional defect, constituting the Eisenmenger complex while 51 had pulmonary stenosis with aortic dextroposition in 32 constituting the tetralogy of Fallot These complications are important in that they favor cyanosis the dextroposition of the aorta is especially significant in this respect The sexes are about equally represented in pure interventricular septal defects of Abbott s series of 50 cases 21 were male 26 were female and the sex of 3 was not stated

The *pure ventricular septal defect* is usually small and more or less circular or oval 1 to 2 cm in diameter (Figures 69 and 70) Its septal edge is often thickened and fibrous and the endocardium of the right ventricular wall opposite the opening is also similarly affected probably by the repeated impact of the blood stream from the left ventricle The right ventricle is usually somewhat enlarged (hypertrophied and dilated) and the pulmonary artery is slightly dilated the left ventricle also may be bigger than normal The shunt through the uncomplicated septal defect is arteriovenous that is, left to right except under unusual conditions

There are no symptoms of pure ventricular septal defects unless they are very large and in rare cases there are no signs Usually however there is a loud blowing systolic murmur heard best just to the left of the midsternum and not widely transmitted When the murmur is very loud there is a palpable thrill also but this is occasionally absent Cardiac enlargement may or may not be evident on physical examination and by roentgen ray The electrocardiogram is normal except in a few cases with abnormal right axis deviation and in rare cases in which the septal defect is associated with abnormality of the atrioventricular bundle (of His) with resulting congenital heart block. Cyanosis is rare in the case of uncomplicated ventricular septal defect and is practically only a terminal condition the shunt being reversed to become venoarterial or right to left when the right ventricular pressure exceeds that in the left ventricle in pneumonia or some other such complication Infrequently when the septal defect is large the whole heart may be much increased in size and fail with characteristic congestive signs and symptoms including dyspnea

An isolated interventricular septal defect has been called *Roger s disease* (Roger 1879) and the murmur caused by this defect has been called *Roger s murmur*

Roger H "Recherches cliniques sur la communication congenitale des deux cœurs par inocclusion du septum interventriculaire" *Bull de l'Acad de med* 1879 2me ser VIII 1074

The following conclusions of this original publication are of interest (translation by myself)

1 There is a *developmental defect of the heart* from which cyanosis does not result in spite of the communication between the two ventricular cavities and in spite of the free mixture of venous blood with arterial blood This congenital abnormality which is compatible even with a long life is a simple one without the coexistence of congenital pulmonary stenosis It consists of a defect (opening) in the interventricular septum

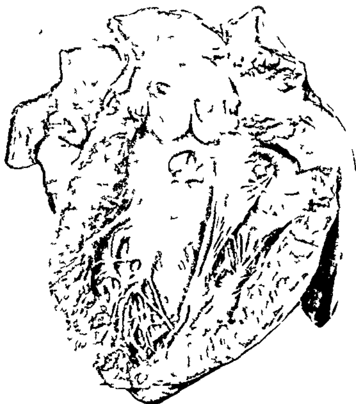


FIG 70 Photograph of the heart of a boy showing a congenital interventricular septal defect of small size just below the aortic valve The child had a typical loud systolic murmur (Roger s murmur) with thrill at the left border of the sternum maximal in *the third and fourth intercostal spaces*

"2 It is important to distinguish this cardiac anomaly which I have recently been the first to study clinically not only from other malformations but especially from acquired heart disease It is revealed only on auscultation by a physical sign with very special characters this is a long loud murmur (produced by the passage of blood through the interventricular opening and directly into the pulmonary artery or the aorta the site of which is frequently abnormal in these cases) This murmur is uncomplicated by other murmurs it begins with systole and is prolonged to such an extent that it entirely covers the natural tic tac of the normal heart sounds It has its maximum intensity neither at the apex (as in the case of

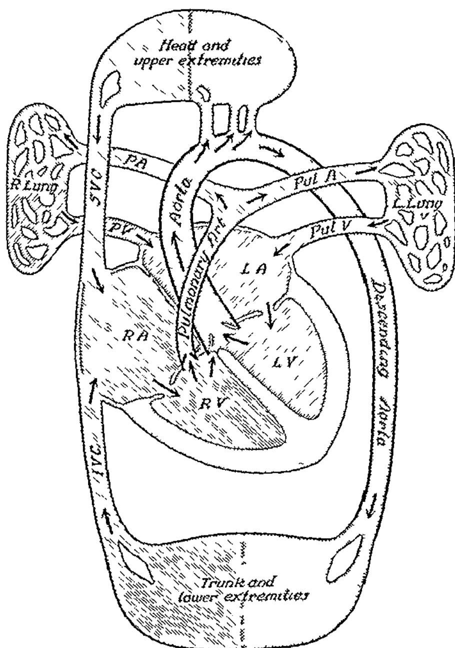


FIG 71 Diagram of tetralogy of Fallot (Kindness of Dr Helen Taussig Johns Hopkins Hospital Baltimore and The Commonwealth Fund New York City)

lesions of the auriculoventricular orifices) nor at the base to the right (as in aortic stenosis) nor to the left (as in pulmonary stenosis) but over the upper third of the precordial region It is chiefly median in position like the septum itself and from this central point it diminishes in intensity uniformly as one moves the stethoscope over the chest The murmur is not transmitted to the vessels It coincides with no other sign of organic disease except the *harsh thrill* which accompanies it This murmur is *the pathognomonic sign of an interventricular septal defect*

3 *The differential diagnosis* of this malformation (until now unrecognized or confused with other congenital or acquired lesions) will be henceforth rendered easy by attentive comparison of the physical signs These signs vary in number site and characteristics in heart disease when structural changes are multiple progressive and changing while the murmur in question like the permanent unchanging lesion causing it remains without modification for an indefinite time The same statement is true in comparing this murmur with signs of functional disorders such signs are very variable according to the diverse periods of cardiac weakness and they are totally dissimilar in their acute or chronic nature from the constant signs of defective interventricular septum which change hardly at all with the years and increase only very slowly and almost insensibly

4 The consideration of the age of the subject is a capital point in the diagnosis endocarditis for example shows itself almost never in infancy before the age of two years and on the other hand the anemia of very young children is almost never attended by a heart murmur The result is that a *murmur in a nursing infant* is almost a certain indication of an *anomaly* of the heart or great vessels

5 The *prognosis* is in general less grave in the malformation described above than in other organic diseases of the heart in which the danger for children is greater and nearer permitting hopes for scarcely more than another decade of life In spite of the presence of an uncomplicated interventricular septal defect individuals can reach and even surpass the average duration of human life

6 An exact diagnosis ordinarily demands in heart disease an active persistent *treatment* If on the other hand there is a congenital malformation of the heart *vigorous treatment is useless and even harmful To show thanks to precision in* diagnosis when to act in one case and when to refrain in another is to render a service not only to physicians but also to patients

It is of interest to note that Roger first described the condition and murmur that go by his name without having correlated in the same patients clinical and postmortem data He had made observations clinically and pathologically but not in the same cases Later however his deductions were confirmed

Although an interventricular septal defect is theoretically not a serious lesion it is a handicap which shortens life In Abbott s series of 50 pure cases the mean duration of life was only 14½ years, the oldest case being 49 years old One of the chief reasons for this shortening of life has certainly been in the past subacute bacterial endocarditis which Gelfman and Levine (1942) found to have complicated 57 per cent of 14 autopsied cases With prophylactic use of penicillin and of other new specific therapy against infections this situation will be radically changed and the prognosis will doubtless be *very much brighter especially since the septal defect itself causes*

relatively little strain on the heart Protection of such a patient is especially needed at the time of dental extraction when 300,000 units of penicillin should be injected intramuscularly 1 hour before the extraction and again 3 hours after to get rid of any alpha hemolytic streptococci that may get into the blood stream If subacute bacterial endocarditis is already present involving the edge of the defect in the right ventricle or the tricuspid valve or adjacent ventricular endocardium opposite the opening penicillin in large dosage (800 000 to 1,000 000 units a day) should be given for several weeks or if ineffective multiplied several times or supported or replaced by streptomycin For details of this therapy consult Chapter 15 Subacute Bacterial Endocarditis

Treatment of a pure isolated ventricular septal defect by surgery was hardly dreamed of when the first three editions of this book were published but now it is only a matter of time before such correction becomes a practical routine already animal experimentation has demonstrated its possibility and the first successful attempts have been made in man (Murray 1948)[4] The technic as described by Murray consisted of introducing a strip of fascia lata into the right ventricle and attaching it to the septum The details of this delicate operation are described by him in the Annals of Surgery, 1948 XXVIII 843

Still more important will some day be the prevention of this as well as other congenital cardiovascular anomalies by the prevention or early cure of diseases virus (like rubella) and otherwise that beset the mother during the critical stage of the fetal heart development in the first trimester of pregnancy

The tetralogy of Fallot This commonest of all combinations of congenital cardiac defects and one of the most serious has already been presented in part as an interesting and characteristic malformation in the early pages of this chapter (page 290 and Figure 64 page 299) but it belongs in the group of ventricular septal defect variations and so will be further discussed here (Figure 71) As noted above the four essentials of this relatively common anomaly are (1) a high ventricular septal defect (2) a dextroposed aorta overriding the septal defect (3) stenosis of the pulmonary valve or of the right ventricular infundibulum below it and (4) a much hypertrophied right ventricle *It was encountered in 85 of Abbott s 1 000 autopsied cases of congenital defects of heart and great vessels There are always* cyanosis and finger clubbing from earliest childhood often intense the cyanosis being increased by exercise which readily distinguishes it from the slaty blue color of argyria which is decreased when the skin flushes after exercise Shortness of breath a tendency frequently to squat weakness and faintness or even syncope are usual symptoms A moderate to loud pulmonary systolic murmur on auscultation blunt shoe shaped heart with prominent aorta and decreased pulmonary vascular shadow on x ray examination (Figure 72) and marked

4 By March 1951 Murray (personal communication) had operated to close ventricular septal defects in 13 cases with clear evidence of success in 7 (disappearance of murmur decrease of heart size abolition of shunt as shown by cardiac catheterization and increase of energy) 3 cases died

right ventricular preponderance by electrocardiogram (Figure 73) complete the diagnostic evidence Polycythemia and excessive hemoglobin even up to double the normal are in accord with the intensity of the cyanosis Cardiac catheterization quickly reveals the dextroposed aorta into which the catheter

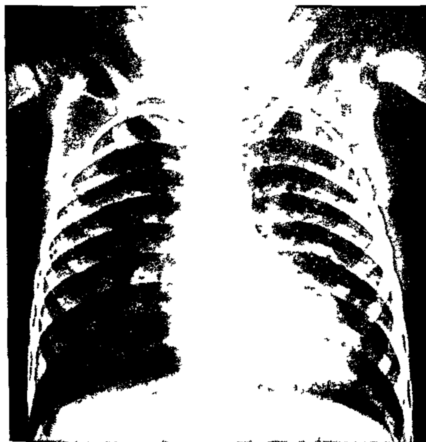


FIG 72 Roentgen film of the thorax in a case of tetralogy of Fallot

readily passes There may be the complication of patency of the ductus arteriosus with the tetralogy of Fallot and if so there is much less cyanosis There is in such cases a continuous murmur to the left of the sternum with the aorta in its ordinary position but with a right sided aorta the murmur is to the right of the upper sternum

The prognosis of the tetralogy of Fallot is generally bad for a long life the average duration in Abbott s series of 85 cases being 12 years but a few patients reach middle age and one established the record of 59 years and 8 months (White and Sprague 1929) Fatal complications include cerebral abscess cerebral thrombosis bacterial endocarditis respiratory infections and right heart failure

The treatment was stated in the first three editions of this book to be only ordinary common sense protection of a cardiac cripple but in the few years that have elapsed since then a great advance has been recorded Blalock and Taussig in 1945 introduced a surgical operation that has greatly ameliorated the symptoms and signs of the disease although they have not cured it The

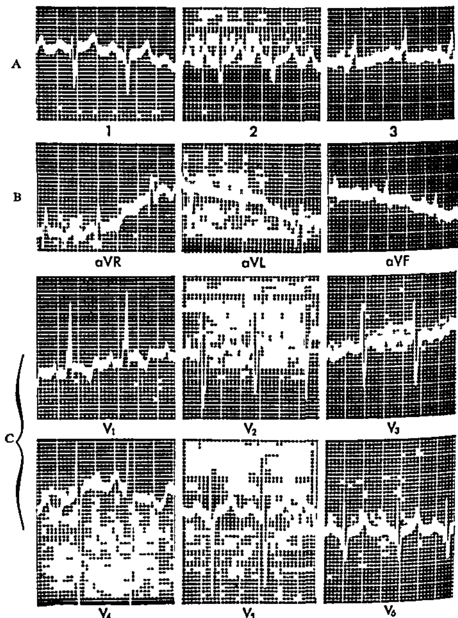


FIG 73 Electrocardiogram in a case of tetralogy of Fallot male age 3 (*A*) Bipolar limb leads 1 2 and 3 (*B*) unipolar limb leads aVR aVL, and aVF (*C*) six precordial leads V to V inclusive Time = 0 04 and 0 ?0 second amplitude 1 mm = 0 10 mv

procedure consists of the anastomosis of the right or left subclavian artery or in a few instances of the innominate artery to one of the pulmonary arteries thereby bringing blue blood into the lungs for oxygenation largely if not wholly relieving the cyanosis dyspnea weakness polycythemia and clubbing of the fingers in a most dramatic way At the time of writing 1 045 cases of the morbus caeruleus mostly consisting of the tetralogy of Fallot or some variation thereof had been subjected to this operation in Blalock s clinic with a mortality of approximately 18 per cent and a high degree of improvement in the majority of the survivors (*Blalock* personal communication *1951*)

Another technic to aid the victims of the tetralogy of Fallot in a similarly effective way has been introduced by Potts (1946) and consists of a somewhat simpler procedure of side to side anastomosis of aorta and pulmonary artery This operation of Potts has one particular advantage over that of Blalock in that it may be easily carried out in very young infants who might readily expire as a result of the tetralogy of Fallot before they reach the age in which Blacock s anastomotic operation is feasible In both types of operation however it should be noted that a new defect has been introduced by the surgical procedure amounting essentially to a left to right shunt which acts like an arteriovenous communication to increase the work of the heart Taussig (1948) has demonstrated by x ray the increase in heart size that follows the operation even while great improvement is shown by the child Also a continuous murmur resembling that of a patent ductus arteriosus results from the operation Despite this unfavorable point the life of these children has undoubtedly been prolonged though just how much it is still impossible to say The most suitable age for either of these two surgical procedures is probably between 6 and 18 although successful results have been noted earlier and later A more recent surgical procedure has been introduced by Brock (1948) and consists of valvulotomy of the stenosed pulmonary valve the clearing of cyanosis has been noted in a few cases but it is still too early to evaluate this therapy

An important though not very common complication of the tetralogy of Fallot is subacute bacterial endocarditis and therefore the same advice about the therapeutic and prophylactic use of penicillin given for a localized pure ventricular septal defect (see above) should apply here

Finally as stated in the general discussion of congenital heart disease the most important consideration of all is that of the prevention of such a malformation as the tetralogy of Fallot This will doubtless depend in large measure on the protection of the mother from various deleterious influences including virus infections (such as rubella) during the first three months of pregnancy

The Eisenmenger complex Another but much rarer variation of the group of ventricular septal defects is that described by Eisenmenger (1897) consisting of this defect overridden by a dextroposed aorta and accompanied by a large right ventricle but with no pulmonary stenosis There were only 7 such cases in Abbott s series of 1 000 in contrast to the 85 patients with the

tetralogy of Fallot The symptoms and signs are much the same however in the two conditions though generally less pronounced in the case of the *Eisenmenger complex* which lacks the loud pulmonary *systolic murmur* and which also shows a *normal or even somewhat prominent* pulmonary vascular tree on x ray examination

The prognosis with this complex is still not good but in Abbott s series was far better than that of Fallot s tetralogy the mean age being 25 years as contrasted with 12 years On the other hand there is as yet no surgical correction here because a considerable amount of blood does go to the lungs the difficulty consists in the equally large amount of blue blood that enters directly into the systemic circulation

Entire absence of the ventricular septum so that the heart is **three chambered (cor triloculare biatriatum)** *or* **two chambered (cor biloculare)** *is rare* Surprisingly efficient circulation is possible even with such marked deformity and cases surviving to adult life are on record Although in these cases there is but one ventricle the course of the two blood streams entering it from the atria is often so directed in relation to their inflow and outflow tracts that they may actually mix but relatively little and so not conduce to much of any cyanosis or immediately serious disability of the circulation In Abbott s series of 5 cases with one ventricle and two atria one lived to be 31 years *old and* the mean age was 6 years *There are usually no murmurs or thrills in such cases the cyanosis may* be but slight or even absent *and the heart may* be but little enlarged rendering the diagnosis difficult or impossible The cor biloculare occurred in 9 of the 1 000 cases of Abbott s series, the mean age at death was 3¼ years and the oldest case lived to be only 16

To be distinguished from a congenital interventricular septal defect there occurs rarely a septal defect due to inflammatory ulceration through the upper septum in bacterial endocarditis or following coronary thrombosis Such *a lesion is relatively small and usually of little importance as a complication of fatal bacterial endocarditis but it is a factor of added and serious and* usually fatal strain in acute myocardial infarction

An interesting and important rare complication of an interventricular septal defect is **congenital heart block** which has never been found without this structural lesion in itself it is not serious and is apparently compatible with a long life and full activity (Campbell 1943) (see Chapter 34)

Anomalous papillary muscles and chordae tendineae In rare *hearts there exist unimportant anomalies of the papillary muscles and chordae* tendineae *for example a papillary muscle found attached to the pulmonary* valve in the routine autopsy of a man 69 years old (Collins 1931) and a chorda tendinea extending across the left ventricular cavity from a small papillary muscle of its own to be attached well up on the aortic cusp of the mitral valve in a man of 40 years (Hamilton and Byers 1899) The only importance of such cases lies in the occasional occurrence of unusual snapping intrasystolic sounds or twanging systolic murmurs which may cause undue apprehension

CONGENITAL MYOCARDIAL DISEASE

The heart muscle may be involved congenitally in a variety of ways The most common change is that of **hypertrophy**, with or without dilatation secondary to various valvular septal and vascular defects (for example pulmonary stenosis large interatrial septal defect coarctation of aorta) This response to increased work and strain is comparable to that found in acquired valvular heart disease and chronic hyperpiesia The muscle fibers are hypertrophied in whatever heart chambers are under particular strain the right ventricle being by far the most commonly affected compared with the situation a decade or two ago There are now but few cases of enlargement of this sort that are unexplained these are grouped as congenital idiopathic hypertrophy There have been slowly separated from this group three other myocardial changes that are of importance One consists of **necrosis and fibrosis** associated with hypertrophy explained on the basis of (1) infection and (2) anoxia and most clearly evident in instances of very faulty anomalous blood supply as for example when the left coronary artery arises from the pulmonary artery A second myocardial change is that of the deposition of glycogen in large amounts in vacuoles in the heart muscle in the so called **glycogen storage disease (von Gierke's disease,** von Gierke 1929 Pompe 1933) here the enlargement and glycogenization of the heart (Figure 74) are but part of the systemic disease of faulty glycogen metabolism with similar involvement of other organs in the body (especially the liver) fasting hypoglycemia failure of hyperglycemic reaction readily elicited ketosis and ketonuria and early death The third myocardial condition recently recognized is the dilatation with secondary hypertrophy occurring in very young infants due to **excessively fast heart rates in paroxysmal tachycardia** (Hubbard 1941) (see Chapter 32)

Congenital idiopathic hypertrophy of the heart One of the least common congenital anomalies of the heart is that which has been called idiopathic hypertrophy The actual number of cases of congenital idiopathic hypertrophy has been steadily shrinking in recent years because of the special studies which have separated from it the rare cases of glycogen storage disease (von Gierke s disease—see above) myocarditis apparently of infectious origin (Kugel and Stoloff 1933) instances of extensive myocardial necrosis with fibrosis such as that occasioned by a very abnormal coronary blood supply (Bland White and Garland 1933) and cardiac enlargement secondary to formerly unrecognized paroxysmal tachycardia of excessively fast rates in infancy (see above and Chapter 32) There still remain a few unexplained cases

The heart in congenital hypertrophy (idiopathic or not) is frequently two or three times the normal weight (75 gm for example instead of 25 gm at the age of 4 months) and may also be considerably dilated In one of our own cases found to be due to glycogen storage disease the heart weight was five

times the normal 175 gm instead of 34 (Figure 74) The cardiac enlargement is easily made out on physical examination and by roentgen ray The heart shadow is uniformly enlarged and roundish in shape prominent to right of the midline as well as to left and without particular dilatation of the atria or great vessels (arteries or veins) The electrocardiogram in uncomplicated cases is not remarkable but with coronary anomalies it may be very abnormal (see end of this chapter)

The male sex is more frequently involved than the female The course is

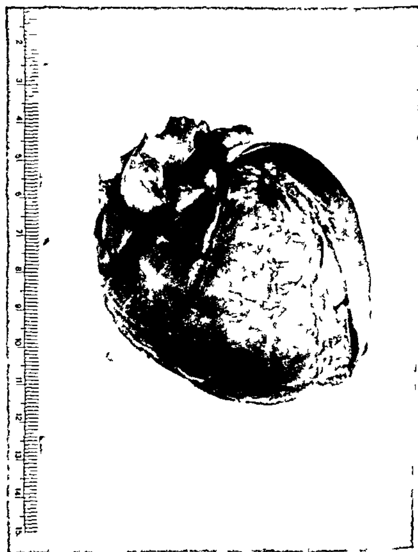


FIG 74 Congenital hypertrophy of the heart due to glycogen storage (von Gierke's) disease This heart of a 7 month-old infant weighed 175 gm instead of the average normal of 34 gm for this age Both ventricles were enlarged but the shape of the heart was not significantly altered from the normal

progressively a downhill one with symptoms and signs of circulatory embarrassment and weakness during the first year of life Death comes rather suddenly or after increasing dyspnea or systemic venous congestion at about six months to a year or two of age the oldest patient of Abbott s series of 10 lived only four years

There is no treatment as yet but further study will doubtless reduce still more the number of cases of congenital idiopathic hypertrophy that are wholly unexplained

CONGENITAL ENDOCARDITIS AND VALVULAR DEFECTS

Although acute endocarditis has been noted in the fetus and in the infant at birth it is the late result of such inflammation that is much more frequently seen and which doubtless explains some congenital cardiac defects Occasion ally in cases with pulmonary stenosis aortic stenosis and other congenital valvular lesions and rarely even in hearts without such lesions the endo cardium lining a part or the whole of a heart chamber may be thick and white due to marked fibrosis the only adequate explanations of which are in most cases a state of chronic anoxia or strain or a fetal endocarditis the deformed valves in such cases are also thickened and scarred as a rule

Any heart valve or chamber may show this abnormality but the pulmonary valve and the infundibulum of the right ventricle are much more commonly involved than any other part of the heart quite probably because of the fact that they bear the brunt of the chief cardiac circulatory effort in fetal life, the aortic valve comes a very late second while the mitral and tricuspid valves are affected only *rarely In Abbott s series of 1 000 cases there were 150* cases of pulmonary or infundibular stenosis or atresia 35 cases of aortic or subaortic stenosis or atresia 19 cases of tricuspid stenosis or atresia and but 11 cases of mitral stenosis or atresia Only rarely except in the cases with aortic valve involvement were the valvular defects uncomplicated the reason for the relatively common uncomplicated occurrence of aortic or subaortic stenosis is probably its late development in the course of intrauterine life Preponderant valvular regurgitation of congenital origin (involving the tri cuspid pulmonary or aortic valve) is excessively rare as is also multiple valvular disease Rheumatic valvular disease may infrequently be found as a complication of congenital heart disease

Pulmonary valve or infundibular stenosis is in the vast majority of cases complicated by septal defects (101 of 110 cases in Abbott s series) most commonly ventricular alone (51 of Abbott s cases) less often both atrial and ventricular (34 of Abbott s cases) and rarely atrial alone (16 of Abbott s cases) Quite often it is associated not only with a ventricular septal defect but also with dextroposition of the aorta and marked right ventricular enlarge ment to form the tetralogy of Fallot (see page 318) The signs course and prognosis vary greatly according to the degree of the pulmonary valve or infundibular stenosis and of the associated anomalies particularly the degree

of aortic dextroposition When pulmonary stenosis is a part of the tetralogy of Fallot cyanosis is invariably present with an atrial septal defect cyanosis *and finger clubbing are less than in the case of the tetralogy* of Fallot but when pulmonary stenosis is independent of septal defects which is a much rarer situation cyanosis is not present until the right heart fails on which occasion stasis in the peripheral circulation is the explanation The characteristic sign of pure pulmonary stenosis is a loud pulmonary systolic murmur with accompanying thrill Congenital pulmonary stenosis has itself in recent years been relieved surgically in a considerable number of cases Valvulotomy was introduced by Brock in 1948 Blalock has followed suit and reports (personal communication 1951) having operated upon 42 cases of valvular pulmonary stenosis with intact ventricular septum with 8 deaths

Congenital pulmonary regurgitation is very rare (see Chapter 26 for signs of this valve defect) it may complicate pulmonary or infundibular stenosis **Pulmonary valve atresia** (closure) is always attended by other compensatory anomalies it allows but a very few years of life as a rule, the mean age in Abbott s 40 cases being 4 years and the oldest 30 years

Aortic valve or subaortic stenosis is one of the rarer congenital anomalies It doubtless is sometimes wrongly diagnosed as acquired aortic stenosis the signs and course of both are outlined in Chapter 26 The valve is no more frequently involved (11 cases of Abbott s series) than the infundibulum of the left ventricle just below the valve (subaortic stenosis) (12 cases of Abbott s series) **Congenital aortic regurgitation** of any high degree has not yet been reported so far as I am aware in slight degree it may complicate aortic stenosis or the dilatation of the aorta encountered in the tetralogy of Fallot **Aortic valve atresia** is incompatible with life for more than a few months at best (maximal age of the 12 cases of Abbott s series 15 weeks mean age 8 weeks) there must of necessity be a compensatory patency of the ductus arteriosus

Mitral and tricuspid valve stenosis and atresia are rare anomalies almost always attended by compensatory septal defects The average duration of life in cases with these anomalies is short The commonest of these defects is tricuspid atresia of which there were 16 examples in Abbott s series the oldest survived to the age of 56 years There were 3 cases of tricuspid stenosis *(the oldest 28 years of age) 6 cases of mitral stenosis (oldest 27 years)*, and 5 of mitral atresia (oldest 3½ years) Clinical recognition of defective development of the right ventricle associated with tricuspid atresia or hypoplasia has been established (Taussig 1936) the diagnostic criteria consist of cyanosis in infancy much diminished roentgen ray shadows of right ventricle and pulmonary artery left axis deviation by electrocardiogram (Figure 75) and absence of murmurs It is to be treated surgically by Blalock s or by Potts operation as in the case of the tetralogy of Fallot (q v for details) In very young infants Potts operation is more suitable than Blalock s and may be lifesaving prior to the time of the arrival at the age when the more complicated procedure is feasible (Gasul et al 1949) **Tricuspid regurgitation**

has been described and is due to displacement of the attachment of the cusps of the valve (Ebstein 1866 Yater and Shapiro 1937)

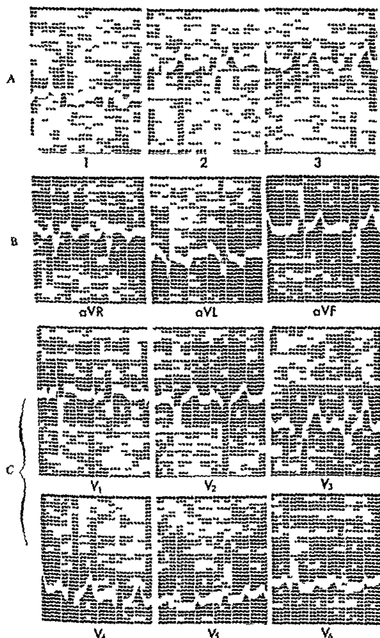


FIG 75 Electrocardiogram in a case of *tricuspid atresia* male age 7 years (*A*) Bipolar limb leads 1 2 and 3 (*B*) unipolar limb leads aVR aVL and aVF (*C*) six precordial leads V to V inclusive Time = 0 04 and 0 20 second amplitude 1 mm = 0 10 mv

CONGENITAL PERICARDIAL DEFECTS

There are several types of pericardial abnormality of congenital origin all rare These include absence or defects of the parietal pericardium (30 cases in Abbott s series), and diverticulum or hernia (6 cases in Abbott s series)

The parietal pericardium may be entirely absent so that the heart lies in the left pleural cavity along with the left lung or it may be defective in part most commonly over the region of the pulmonary artery In the case of ectopia cordis there may or may not be a pericardial sac the cases with better prognosis have such a sac When the parietal pericardium is absent the heart is usually freely movable both on respiratory movements and with changes of body position physical examination and especially roentgen ray study may reveal this extreme mobility The clinical significance of absence or defect of the parietal pericardium is practically nil in itself normal duration and activity of life being possible without any cardiac strain or circulatory embarrassment Two complications may arise however One is due to close contact of heart with left lung and pleura so that disease of the latter may seriously affect the former and vice versa there no longer being protection by an intervening cavity Pleurisy with effusion empyema and pneumonia have been reported as fatal illnesses in the cases on record with absence or deficiency of pericardium Another complication of importance that has been reported resulting in pain or even death is sudden kinking of the great vessels due to the fact that the heart is so freely movable

The other two congenital anomalies of the pericardium diverticulum and absence of attachment are very rare and of no clinical importance when they do occur except that occlusion of the orifice and consequently distension of the cavity of a pericardial diverticulum may interfere somewhat with the heart s action

CONGENITAL ANOMALIES OF THE AORTA

Congenital aortic anomalies found mostly in young persons are due to maldevelopment in fetal life or at birth and include hypoplasia coarctation right aortic arch double aortic arch aneurysms and transposition of th aorta and pulmonary artery as well as septal defects between aorta and pulmonary artery right ventricle or auricle and patency of the ductus arteriosus

Aortic Hypoplasia

Hypoplasia (ὑπό under and πλάσις formation) or small caliber of the aorta throughout its course is one of the commonest of the congenital aortic anomalies but in high degree it is relatively rare and it is then usually associated with other congenital cardiovascular defects In Abbott s series it was found in

77 cases 75 of which showed other defects the commonest associated abnormality was an atrial septal defect With such a defect there is a combination of a very large pulmonary artery and a small aorta due to the overloading of the pulmonary circulation and the underloading of the systemic There is general hypoplasia of the arterial system when there is much aortic hypoplasia with a tendency to pallor slow and incomplete growth and retardation of sexual development Small heart size and large heart size have both been reported in this condition and heart failure in youth is said to have resulted from the strain due perhaps in part to a high degree of aortic narrowness but more probably to complicating congenital defects in the heart itself

Coarctation of the Aorta

Coarctation (*co-* together and *arctare* to press or make tight) of the aorta is a localized narrowing of the aorta of greater or lesser degree in the vicinity of the insertion of the ductus arteriosus which sometimes remains patent Morgagni (1761) was the first to record its discovery at autopsy It is a fairly common abnormality having been noted in 142 of Abbott s series of 1 000 cases of congenital cardiovascular defects in 79 of which it was the primary lesion and in the other 63 a complication of other anomalies slight grades are likely to be missed even on postmortem examination and are of no clinical importance

Etiology and pathology There have been described two chief types of aortic coarctation called the infantile and the adult but there is not always a sharp separation between them The first (or infantile) a rare type (37 cases in Abbott s series only 9 of which were primary) consists of narrowing of the whole isthmus that is that part of the aorta between the left subclavian artery and the ductus arteriosus sometimes the proximal arch itself is also involved In fetal life the isthmus has little function since blood enters the descending aorta largely through the ductus arteriosus therefore it quite naturally remains hypoplastic This fetal condition may persist for a few weeks or months after birth to a greater or lesser degree but rarely is it found in adult life In extreme cases it may be represented simply by a fibrous cord the circulation to the lower part of the body being taken care of wholly in such cases by the patent ductus arteriosus which thus supplies only venous blood to the abdominal viscera and legs with resulting disability The infantile type is serious usually associated with other important anomalies and had been thought to be incompatible with long life there having been a maximum of 9 months and a mean of 8 hours in Abbott s series of 9 primary cases However recently Johnson and Kirby (1948) have reported using in three patients aged 13 17 and 20 years respectively the left subclavian artery to bridge the long gap of the coarcted aorta of the infantile type with success in one case partial benefit in a second and failure in a third

The second (or adult) type of aortic coarctation consists of localized constriction of the aorta at or most often just below the insertion of the ductus

arteriosus and rarely above that point (Figure 76) It is much more common than the infantile type and less serious in Abbott s series there were 105 cases in only 35 of which the condition complicated other defects It is probably always a prenatal condition developing in the fetus In only a few of the cases does the ductus arteriosus remain patent There mav be other congenital cardiovascular anomalies especially when the coarctation is extreme

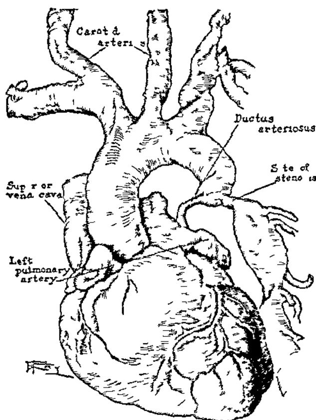


FIG 76 Coarctation of the aorta (adult type) just below the ligamentum arteriosum (Case of Dr W D Shelden) (Blackford Coarctation of the Aorta *Arch Int Med* May 1928)

but frequently the condition is uncomplicated The most common associated anomaly is the bicuspid aortic valve either congenital or acquired in origin found by Abbott in 50 out of 183 collected cases (Abbott 1928) and in 4? per cent of 104 additional autopsied cases reported by Reifenstein et al in 1947 All grades of narrowing of the aorta occur from that which is so slight that it can scarcely be seen on careful postmortem scrutiny up to complete local aortic obliteration Coarctation has been noted more often in the male than in the female the adult type being three to five times more frequent in the male sex why this is so is not known In a recent series of 96 cases reported at the Mayo Clinic (Christensen and Hines 1948) there were 76

males and 20 females this ratio is characteristic of other series It has also been found in more than one member of a certain family (Walker 1934)

The result of pronounced coarctation of the aorta of the adult type on the circulation is of much interest The aorta is usually considerably dilated above the constriction (sometimes with an aneurysm) and often but not always narrowed below A collateral circulation is developed at times in high degree blood being carried to the lower part of the body by widely dilated tortuous internal mammary scapular and intercostal arteries The heart becomes en larged in most cases and sometimes is markedly hypertrophied and dilated Hypertension accompanying the coarctation is responsible for this cardiac hypertrophy as a rule but on occasion acquired valvular disease which is a not infrequent complication may be an additional factor The arterioles in the muscle and skin of the arms in young subjects are normal and indis tinguishable from those in the legs (Graybiel Allen and White 1935) The hypertension usually found in persons with aortic coarctation need not be wholly ascribed to the defect directly but may be due in part at least to a secondary effect namely the diminution of the renal blood flow below the con striction which in turn causes a generalized vasoconstriction reflexly or through the production of the chemical mediator called hypertensin or angiotonin (see Chapter 19) (Steele and Cohn 1938) when the collateral circulation is very richly developed the blood pressure may be perfectly normal the renal circulation also then being adequate The early hypertension in cases of aortic coarctation is sometimes attended by congenital intracranial aneurysms (as in the circle of Willis) Also unusual blood supply to the teeth has been re ported in coarctation of the aorta

Symptoms and signs There are no particular symptoms of the adult type of coarctation of the aorta and often no signs or so slight that the anomaly escapes notice during life With high grades of coarctation however there are a number of important signs (1) inequality of blood pressure and of pulse fullness and form between the upper and lower extremities the brachial systolic pressure often being much elevated (even to 200 mm of mercury or more) while the femoral blood pressure is low (100 mm or less as a rule) and the femoral pulse is small although the diastolic pressure levels may be much the same (2) evidence of compensatory collateral circulation between the upper and lower parts of the body the internal mammary intercostal scapular and deep epigastric arteries being much dilated tortuous and in the case of the first three groups of vessels easily felt and sometimes visibly pulsating (3) long systolic murmurs transmitted from the aortic coarctation itself heard not only over the precordium and back but especially down the spine where it may be heard to extend into diastole and also along the course of the dilated tortuous anastomotic vessels sometimes accompanied by palpable thrills (4) decrease or absence of the shadow of the aortic knob by roentgen ray frequently with dilatation of the ascending aorta and first part of the arch (5) roentgen ray evidence of well marked notching of the ribs due to the dilated tortuous intercostal arteries (Figure 77) and (6) enlargement of

the heart and sometimes signs of failure due in part to frequent complicating heart lesions (especially acquired valvular disease) but in large part to the hypertension associated with the stenosis of the aorta It should be reiterated that the brachial systolic pressure is not always high in cases of coarctation of the aorta but there is almost always a greater blood pressure in arms than in legs Retrograde arterial or direct aortic Diodrast injections can helpfully outline the roentgen ray shadow of the coarcted aorta and of some of the collateral circulation for confirmation of the diagnosis and especially as guidance for the surgeon

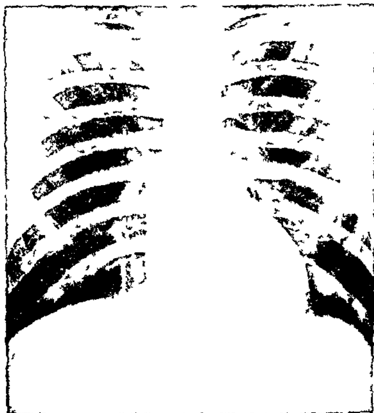


FIG 77 X ray photograph of a 19 year-old boy with coarctation of the aorta demonstrating notching of the ribs and absence of aortic knob (Blood pressure in the arms 175/110 blood pressure in the legs 135/100)

Course and prognosis Complications The course and prognosis of coarctation of the aorta vary enormously depending chiefly on the degree of narrowing of the aorta and the extent of the collateral circulation but even when slight the condition is important because of the possibility of local infection in the form of subacute bacterial aortitis or endocarditis of a bicuspid aortic valve Marked coarctation is often a serious anomaly which may kill in youth by one of four complications heart failure rupture of the aorta itself apo-

plexy due to cerebral hemorrhage or thrombosis and bacterial infection invading the area of coarctation or the aortic valve On the other hand it is compatible with long life as in the case of a 92 year old man with completely closed aorta (Abbott 1928)

Of a series of 200 cases of the adult type collected by Abbott (1928) the average age at death was close to 32 years with extremes of 3 and 92 years 60 died of congestive heart failure 40 of sudden heart (2) or aortic (38) rupture 26 of cerebral complications and 14 of bacterial endarteritis Of a more recent series of 104 autopsied cases (Reifenstein et al 1947) 23 per cent died of rupture of the aorta 22 per cent of bacterial invasion 18 per cent of congestive heart failure 11 per cent of intracranial lesions and 26 per cent of incidental causes

Between 5 and 10 per cent of cases with coarctation of the aorta have an associated patency of the ductus arteriosus for example 8 of 140 cases surgically treated by Gross (personal communication 1950) 10 per cent of a series at the Mayo Clinic (Taylor et al 1950) and 10 per cent of Abbott s cases

Treatment In the last edition of this book it was stated that there was no special therapy for congenital coarctation of the aorta but that the subject should be protected as much as possible from physical strain and infections In the intervening years there has occurred a great advance due to the introduction independently by Crafoord (1945) and Gross (1945) of surgical correction of the defect by excision of the area of coarctation and end to end anastomosis of the cut ends of the aorta in children and young adults where the narrowed portion is long the left subclavian artery or a vascular graft can be used to bridge the gap Postoperatively the blood pressures in arms and legs equalize at normal levels Of the first 100 cases operated upon by Gross (1950) 11 died and they were for the most part early cases of the others 71 were completely relieved 8 others satisfactorily improved one unchanged and 9 explored only (because of findings contraindicating operations on the aorta itself) Blalock has written to me (February 1951) of having operated upon 103 cases of coarctation of the aorta with 11 deaths

Differential diagnosis There is one condition with which coarctation of the aorta is commonly confused and that is hyperpiesia (essential hypertension) The differentiation is however easy if one has in mind the possibility of the congenital defect especially in a child or young adult the difference between the blood pressures of arms and legs the systolic or continuous murmur transmitted down the upper spine the palpable intercostal artery pulsations and the notching of the ribs seen by roentgen ray at once lead to the correct diagnosis

Other Rare Congenital Aortic Anomalies

These are (1) localized weakness of the wall resulting in aneurysms usually small (2) transposition of the aorta and pulmonary artery so that the former

arises from the right ventricle and the latter from the left as the result of reversed torsion of the common arterial trunk in the course of fetal development (3) a right sided instead of a normal left sided aortic arch and (4) a double aortic arch due to persistence of the right hand side of the fourth primitive arch

Congenital defects in the aortic wall Congenital defects in the aortic wall with thinning and even outpocketing (aneurysm) are very rare and small They are an incidental finding at postmortem examination and are of no clinical importance The medial necrosis responsible for dissecting aneurysms does not belong here

Transposition of the great arteries Transposition of the great arteries is an infrequent anomaly found much more often in the male sex than in the female in the ratio of about 4 to 1 It is incompatible with survival for more than a few hours or days after birth unless there is a septal defect which allows some venous blood to reach the lungs such defect usually consists of a patent foramen ovale In some cases there is also an interventricular septal defect or a patent ductus arteriosus When the ventricular septum is defective life may last for years but the handicap is a serious one and death occurs almost always before adult age is reached and is due to heart failure or complicating infections In Abbott s series of 1 000 cases of congenital cardiovascular defects there were 74 cases of complete transposition of the aorta and pulmonary artery in 49 of which it was the primary defect Of these 49 cases, 32 had a closed ventricular septum with longest survival to 11 years while 17 had a ventricular septal defect with longest survival to 16 years

Cyanosis is an almost invariable sign of complete transposition of aorta and pulmonary artery except in early infancy when the cyanosis tends to be absent or less marked than later as is the case also in some other congenital cardiac anomalies the cyanosis sometimes becomes very marked and it is then accompanied by definite clubbing of the fingers The heart is enlarged particularly the right ventricle and the electrocardiogram shows abnormal right axis deviation Roentgenologic study may show little except the cardiac enlargement but there may be some suggestion of the anomaly of the great arteries especially in the oblique views There may or may not be heart murmurs and thrills dependent on the presence of other anomalies such as patency of the ductus arteriosus uncomplicated transposition of the great arteries should not cause murmurs

The antemortem diagnosis of complete transposition of the aorta and pulmonary artery is extremely difficult but Taussig (1938) has pointed out the combination of four characteristic features (1) persistent cyanosis (2) cardiac enlargement especially of the right ventricle (3) a narrow aortic shadow *in the anteroposterior roentgenogram and (4) an increase in the* width of the roentgenographic shadow cast by the great vessels when the patient is placed in the left anterior oblique position

A hopeful development in these very serious cases has taken place since the last edition of this book was published through the introduction by

Blalock of the production of an atrial septal defect and sometimes in addition the anastomotic operation which he has used in cases of the tetralogy of Fallot namely joining subclavian and pulmonary arteries on the right He has operated upon 62 cases with 38 deaths the best results have been in patients with pulmonic stenosis as well as transposition and in patients with the Taussig Bing syndrome (Blalock personal communication 1951)

Corrected transposition of the great vessels There is a condition called corrected transposition of the great vessels in which the aorta and pulmonary artery although in abnormal position regarding each other arise nevertheless from the correct ventricles Such an anomaly in slight degree is of little or no clinical importance since the circulation is maintained practically in a normal manner and the condition may not be very obvious even at postmortem examination When of marked degree however it is associated with other anomalies such as interventricular septal defects and life does not last beyond early adult years there were but 6 cases in Abbott s series 4 of which were primary in type with longest survival to 24 years

Finally a third type of transposition occurs called **partial transposition** in which both aorta and pulmonary artery arise from the same ventricle As in the case of complete transposition with septal defect there is frequently cyanosis Life is usually short in this condition averaging 4½ years in 16 primary cases collected by Abbott

Right or double arch Vascular ring Anomalies of the aortic arch consisting of a right or double arch are rare and for the most part unimportant except that there tends to be more or less compression of esophagus and trachea between the aorta and ductus arteriosus in the case of the right aortic arch and between the two sides of the arch when it is double In some cases this obstruction is an important complication and rarely it may be serious with *dysphagia* (called *lusoria* from the Latin meaning deceitful) esophageal dilatation and ulceration tracheal stenosis and asphyxia With obstruction of high degree and the diagnosis of right or double aortic arch established surgical cure by transecting the constricting vascular ring has been effected by Gross (1945) since the last edition of this book was published Dysphagia lusoria has also been noted in cases with certain other anomalies of the great arteries for example when the right subclavian comes off the descending thoracic aorta instead of the innominate artery The diagnosis must rest in the main at least on roentgen ray evidence of reversed position of the aortic arch or of its double character and on abnormal deviation or obstruction of the trachea and also of the esophagus as studied fluoroscopically during the ingestion of barium (Figure 78)

In Abbott s series there were but 5 cases of double aortic arch the oldest surviving to 87 years and 35 cases of right aortic arch 14 classified as primary with the oldest case 61 years females outnumbered males (8 to 5) in a small series of 13 cases of these two anomalies Abbott recorded 7 cases in her total collection of 1 000 who showed the right subclavian artery arising from the descending aorta and 8 cases with left subclavian artery arising

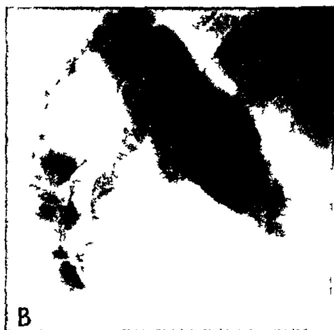


FIG 78 Roentgenograms showing a right aortic arch displacing trachea and barium filled esophagus forward and to the left (*A*) Anteroposterior view (*B*) right anterior oblique view (Kindness of Dr Hugo Roesler Temple University Philadelphia)

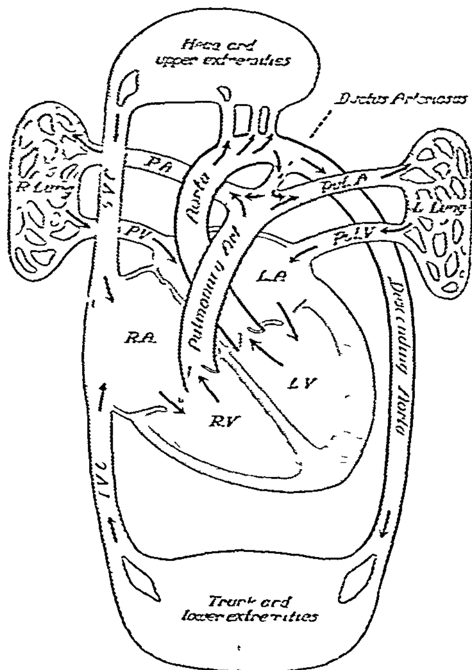


FIG. 79. Diagram of patent ductus arteriosus. (Courtesy of Dr. Helen Taussig, Johns Hopkins Hospital, Baltimore, and The Commonwealth Fund, New York City.)

from either the ductus arteriosus or the pulmonary artery in the former group one of 5 cases lived to be 44 the oldest age noted while the one case of the latter whose age at death was noted was only 5 years old

COMMUNICATIONS BETWEEN THE AORTA AND PULMONARY ARTERY

There are four types of congenital communication between the aorta on the one hand and pulmonary artery right ventricle or right atrium on the other hand They are first and most common patency of the ductus arteriosus second rare cases of a persistent truncus arteriosus without separation into aorta and pulmonary artery third very rare instances of communication between the aorta and pulmonary artery by arterial septal defect and fourth very rare cases of communication between aorta and right ventricle or right atrium by septal defects The possible rupture of the aorta into right ventricle or right atrium in bacterial endocarditis and endarteritis or into the pulmonary artery in syphilitic aortitis is discussed elsewhere (see Chapters 15 and 28 respectively)

Patency of the Ductus Arteriosus

The ductus arteriosus (also called *ductus Botalli* Botallo 1530) which normally in the fetus diverts most of the blood from the pulmonary artery into the aorta *should cease to function soon after birth it should be con*verted within a few weeks into a fibrous cord the *ligamentum arteriosum* Its obliteration may however be delayed for some months or it may persist as a patent arterial canal throughout life Its patency may be regarded as a con genital anomaly if it is found later than three months after birth (Figure 79) It is one of the commonest of all congenital cardiovascular defects ranking third in incidence (242 cases 92 as the primary and 150 as a complicating defect) after interatrial and interventricular septal defects respectively in *Abbott s series of 1 000 cases Because of its curability now in childhood* physicians in general have become much more familiar with its diagnosis For the anatomic position of the ductus arteriosus see Figure 76 page 330

Etiology *Cause* The cause of persistent patency of the ductus arteriosus is not always clear Frequently it appears to be a compensatory condition in the presence of some serious cardiovascular defect like infantile coarctation of the aorta or transposition of the great arterial trunks in other cases it is due to an unexplained arrest of development

Age Beginning at birth it may last through a long life It has been noted most often in children and young adults the mean age at death of 92 cases of simple patency in Abbott s series being 24 years It is frequently found in old people the oldest autopsied cases on record being 66 years (Josefson 1897 White 1928) a man with this condition still in good health at 75 years has been followed by the author for 27 years while another case reported by Walker and Ellis in 1941 then in good health at the age of 73 died suddenly

at the age of 78 five years later while mowing his lawn (there was no autopsy—personal communication)

Sex Patency of the ductus arteriosus has been found more often in the female sex in the ratio of 2 to 1 (55 to 29 in Abbott s series of 92 cases of simple patency in which the sex was stated and 333 to 145 in Gross series of 478 cases—Gross personal communication 1951)

Pathology The patency of the ductus arteriosus varies very much in degree, from that of a fine canal barely admitting a small probe or bristle to that of large caliber easily admitting pencil or finger It may be very short so that there is hardly more than a direct opening between contiguous aorta and pulmonary artery or it may be several centimeters long usually it is ½ to 2 cm long It may be cylindrical in shape funnel shaped or conical with wider end at the aorta or it may be dilated to form a kind of aneurysm In patency of the ductus arteriosus of long duration or of marked degree especially in the combination of these conditions the pulmonary artery is dilated and both ventricles are enlarged with hypertrophy and dilatation the blood flow from aorta to pulmonary artery increasing the work of both ventricles in such cases the right ventricle has to overcome the pressure directed against its own blood stream and the increased blood flow through the lungs and the left ventricle has to increase its output to make up for the diversion of a considerable amount of blood from the systemic circulation It has been estimated that as much as 25 to 75 per cent of the blood pumped out by the left ventricle may be diverted into the pulmonary circulation via a patent ductus arteriosus Atheroma with calcification is commonly found in the patent ductus arteriosus especially at its mouth in the aorta and often also about its orifice in the pulmonary artery *Very rarely spontaneous thrombosis may obliterate the ductus*

The ratio of complicated to uncomplicated patency of the ductus arteriosus is about 2 to 1 In Abbott s series of 150 complicated cases it was found associated with coarctation of the aorta 13 times (6 out of 70 cases of the adult type 7 out of 9 of the infantile type) with complete transposition of the great arterial trunks in 33 cases with pulmonary atresia 28 times with pulmonary stenosis 12 times and with tricuspid atresia 6 times

The ductus arteriosus may take an anomalous course or even be entirely absent Rarely it gives off the left subclavian artery

Symptoms There are no symptoms of patency of the ductus arteriosus itself except in a rare patient who is conscious of the harsh murmur and thrill caused by the rush of blood through the ductus and in occasional cases where the ductus is so large that there is retardation of growth or when dyspnea develops because the heart fails as it would from aortic regurgitation or a large arteriovenous communication

Signs Usually pathognomonic evidence of the condition is present There are two important signs one diagnostic the other suggestive when both are present *the diagnosis of patent ductus arteriosus may be regarded* as certain

The first sign is a continuous murmur usually loud with systolic accentuation maximal over and often limited to the region of the pulmonary artery

at the second rib and intercostal space just to the left of the sternum and not so loud in the neck and generally attended by a palpable thrill (in the absence of evidence of rupture of aorta into pulmonary artery) This murmur has been variously described as resembling the sound of a humming top of a mill wheel or other machinery of a train in a tunnel or of rolling thunder It is almost invariably harsh rarely blowing In cases with a right aortic arch the continuous murmur is heard over the patent ductus at the right of the upper sternum instead of at the left In some cases with wide ductus patency and a dilated left ventricle there may also be heard a mitral middiastolic murmur simulating mitral stenosis

The second important sign is roentgenologic consisting of unusual prominence of the heart shadow in the region of and just above the pulmonary artery (Figure 80) without increase in the size of the left atrium pointing to mitral stenosis and without cyanosis which might result from pulmonary endarteritis obliterans This abnormal bulging of the left upper border of the heart shadow is more pronounced in some cases of patency of the ductus

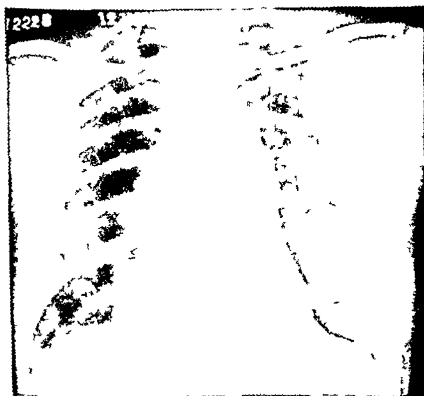


FIG 80 Roentgenogram of thorax in case of congenital patency of the ductus arteriosus Note the bulge in the region of the pulmonary artery J W male now 75 years with characteristic machinery murmur This film was taken 13 years ago but there has been no change since

arteriosus than in any other condition except that of interatrial septal defect which presents much larger shadows of both pulmonary artery and lung hilus shadows without a continuous murmur If there is but a narrow lumen through the patent ductus the roentgen ray sign may be minimal or absent while the typical murmur may be marked If on the other hand there is a very wide lumen with much blood flow the roentgen ray sign is marked and the murmur minimal or absent. In infants and rarely in young children the murmur may be absent or but slight and only systolic in time during the first few years of life in adults it is almost invariably present as a typical continuous murmur, but there are rare exceptions with systolic murmur alone

Other signs are those associated with cardiac enlargement which is found in some of the cases various complications and in a few cases a full pulse pressure due to low diastolic pressure when the patency is so wide that there *is considerable aortic regurgitation into the pulmonary artery in* diastole a wide pulse pressure in patency of the ductus arteriosus is however not the rule and a water hammer pulse is very rare

Course, complications, and prognosis *Patency of the ductus arteriosus may* be a condition compensating for the presence of some serious congenital defect like transposition of the great arterial trunks thereby helping together with septal defects to prolong life, in such cases however *life is short at best* lasting only a few years Uncomplicated patency may or may not be an important burden for the heart If it is of large caliber it is a serious condition leading to considerable cardiac enlargement and failure in youth if it is of small caliber it may limit neither activity nor duration of life death in old *age being caused by some noncardiac disease The oldest cases* proved at autopsy were 66 years of age at death but two other cases have been known to have reached the middle or upper seventies (see above under etiology a*e) Always however patency of the ductus arteriosus is something of a menace because of the likelihood of invasion by subacute bacterial (Streptococcus viridans) endarteritis which used to end fatally in the course of months just as did subacute bacterial endocarditis with which it may be associated In Abbott s series of 92 primary cases of ductus arteriosus patency death was ascribed to subacute bacterial endarteritis in nearly one quarter while Gelfman and Levine (1942) found 4 such cases (29 per cent) among 14 patients with patency of the ductus

Rupture of a dilated pulmonary artery due to ductus arteriosus patency has been observed as a rare complication Also paradoxical embolism has been noted thrombi from the left atrium or vegetations from the mitral or aortic valves entering the pulmonary circulation by way of the patent ductus *arteriosus A reversal* of current may sometimes occur generally as a terminal event when the blood pressure in the pulmonary circulation for any reason exceeds that in the systemic circuit in infants there may be transient attacks *of dyspnea and cyanosis* when the pulmonary pressure is raised by crying and *by holding the breath during nursing* Of 92 cases of Abbott s series death in 40 was sudden or due to myocardial failure in 21 to bacterial endarteritis or

endocarditis in 3 to a cerebral lesion in 3 to bronchopneumonia and in the remainder unstated

Treatment A decade ago there was finally introduced what had been prophesied namely specific treatment for patency of the ductus arteriosus Surgical interference to ligate the ductus was successfully accomplished and a new and dramatic era in the treatment of congenital heart disease began (Gross and Hubbard 1939) The operation has now been carried out in many hundreds of cases by various surgeons throughout this country and abroad with very low mortality and with excellent results Transection rather than simple ligation is now recommended by Gross (1947) although excellent results have been obtained by ligation Surgical correction is now definitely indicated in all children and young adults to relieve the heart of strain and to avert the dangerous and common complication of subacute bacterial (Streptoccus viridans) endarteritis but it must be recognized that there are some patients in whom the condition is inoperable (Shapiro and Keys 1943) and that there still exists in any case a definite operative risk Surgery has also been proved (Touroff and Vesell 1940 and 1942 Bourne 1941) to have a place with or without chemotherapy in the cure of subacute bacterial infection of the ductus and pulmonary artery It is striking to note the disappearance of murmur and thrill after ligation of the ductus and in those cases with cardiac enlargement and increased pulse pressure even of such signs too and on occasion even of a mitral middiastolic murmur due to left ventricular dilatation In those cases not operated upon protection against infection and exhaustion is advisable The routine use of penicillin to ward off bacterial endarteritis during infections and surgical procedures including tooth extraction is to be recommended as in the case of a ventricular septal defect (q v)

Differential diagnosis In infants the condition may be undiagnosable In adults the distinctive murmur is almost invariably present this murmur must be differentiated from the venous hum sometimes heard in the neck especially on the right side in children which hum may be transmitted downward over the upper chest but is quickly obliterated by compression of the neck veins and it must also be distinguished from the murmur of an arteriovenous aneurysm uncommon in the upper chest and usually located on the right side A rare condition accompanied by the continuous murmur characteristic of patency of the ductus arteriosus both in position and in character is rupture of an aortic aneurysm into the pulmonary artery the differentiation can be made by analysis of the clinical course The roentgen ray sign of marked prominence of the pulmonary artery though helpful is not pathognomonic of patency of the ductus arteriosus for mitral stenosis pulmonary fibrosis or endarteritis obliterans and interatrial septal defects must be excluded before a sure diagnosis is justifiable

Other Communications Between Aorta and Pulmonary Artery

The other communications between aorta and pulmonary artery are much less common The first is the serious condition of a common arterial trunk (truncus arteriosus communis) with its accompanying intense cyanosis absence of lung hilar shadows, and short life (averaging but 4 years in 21 cases analyzed by Abbott) A second is an opening between these two vessels above the valves usually small and not so important (in Abbott s series 10 cases with survival to 48 years in the oldest) The third is a defect between the right sinus of Valsalva and the right ventricle with or without an associated slight interventricular septal defect just below the valve or between the posterior sinus and the right atrium The defect may exist from birth or there may be in early life simply a thinned wall or aneurysm which may rupture fatally into the right ventricle (Hirschboeck 1942) There are no symptoms caused by these anomalies The signs in cases of the second and third categories above in which there are definite though small openings are much like those of patency of the ductus arteriosus with loud continuous murmur lower in position and very near the ear The cardiac strain results in enlargement but the particular danger appears to lie in a serious complication of bacterial infection of the walls of the defect

CONGENITAL ANOMALIES OF THE VEINS

Congenital anomalies of the veins are of little or no clinical importance They are frequent in the case of the small veins and rare in the case of the venae cavae and chief pulmonary veins The commonest defect of the great systemic veins is persistence of the left superior vena cava emptying into the right atrium by way of the coronary sinus (36 cases in Abbott s series 27 of which complicated other defects) associated with it in most cases is the usual (right) superior vena cava, but sometimes it is alone and receives blood from the right side by way of an extensively developed vena azygos major In rare cases the single superior vena cava or the inferior vena cava is displaced to the left and opens into both atria at the point of a septal defect Rarely also the left hepatic vein persists and empties into the anomalous left superior vena cava which thus represents the persistent left sinus venosus of the embryo Many different variations are possible in the case of the pulmonary veins (58 cases total in Abbott s series all but 4 complicating other defects) The two right or two left veins sometimes coalesce before entering the left atrium or one or more of the pulmonary veins may empty into the right side of the heart into the persistent left superior vena cava into the normal superior vena cava or into the innominate or hepatic vein *Almost always* there are cardiac anomalies associated with congenital abnormalities of the venae cavae and with the more important abnormalities of the pulmonary veins Symptoms signs course and prognosis depend on these other anomalies and not on the venous defects The diagnosis of uncomplicated congenital defects of the great veins has now become possible in some cases by

means of cardiac catheterization and by detailed x ray studies including angio cardiography

CONGENITAL ANOMALIES OF THE CORONARY VESSELS

Most anomalies of the coronary arteries and veins are of no clinical im portance and are simply postmortem curiosities These include extra coronary mouths (for example the left circumflex coronary artery may arise directly from the aorta) one coronary mouth giving rise to both right and left coronary arteries and unusual course and branching of the vessels Rarely however a serious anomaly occurs this consists most frequently of the origin of the left coronary artery from the pulmonary artery which results in cardiac enlarge ment with hypertrophy and dilatation of the left ventricle myocardial necrosis and fibrosis and early death in the course of the first few months of life One notable case was of a baby boy dying at the age of four months who suffered from attacks during life which closely resembled angina pectoris and showed an electrocardiogram with inverted (coronary) *T* waves in Leads 1 and 2 (Bland White and Garland 1933) Other cases have since been reported one diagnosed antemortem (Eidlow and Mackenzie 1946)

The most common important anomaly of the coronary veins is the per sistence of the left superior vena cava (mentioned above) which takes the place of the coronary sinus this anomaly has however no clinical significance A very rare anomaly is the drainage of the coronary sinus into the left auricle

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SEE ALSO GENERAL REFERENCES FOLLOWING CHAPTER 2 AND REFERENCES IN CHAPTERS 7 AND 9

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CHAPTER 14

RHEUMATIC HEART DISEASE

Introduction Although at present apparently and happily on the decline one of the three most common and serious types of heart disease is rheumatic, the other two are hypertensive and coronary The relative incidence of these types varies greatly in different parts of the world in fact in different parts of the United States of America for example in New England more than twenty years ago the proportions were recorded as approximately **40,** 29 and 36 per cent respectively with some overlapping of the latter two (White and Jones 1928) in Virginia **22,** 46 and 46 per cent respectively (Wood Jones and Kimbrough 1926) in San Francisco somewhat more recently **22,** 22 and 40 per cent respectively (Geiger et al 1936), and in Texas **10,** 45 and 24 per cent for the whites and **4,** 51 and 6 per cent for the Negroes (Stone and Vanzant 1927) A reappraisal of these percentages is now in order because of the possibility of a changing incidence as well as of more accurate statistics Recent papers for example report **13 8** per cent among 436 cases of organic heart disease for Southwestern Virginia (Glendy 1948) 117 cases of rheumatic heart disease (**11** per cent) as found among 1 045 cardiac autopsies in another southern group (Holoubeck and Holoubeck 1947) and **26 9** per cent of 519 cardiacs in the Rocky Mountains (Cannon 1946) A recent review of 3 000 cases of heart disease in New England (White 1951) has given percentages of **23 5,** 26 2 and 48 5 respectively for rheumatic hypertensive and coronary heart disease Thus climatic conditions and to a much less extent race have seemed to be important controlling factors as will be noted in more detail later Other relationships that have become more and more evident in the past few decades are familial susceptibility social and economic status with particular reference to crowding and the hemolytic streptococcus as an exciting factor these will be discussed shortly

One of the most important reasons why rheumatic heart disease is so serious is the fact that it is particularly a disease of youth crippling and killing many children and young adults As a result many medical investigators and special

practitioners and social workers have undertaken campaigns to study the various problems involved and to reduce this menace and scourge which has assumed somewhat the role once held by the white plague tuberculosis During the fifteen year age period from 5 to 20 rheumatic fever with heart disease is in the United States the leading cause of death and at ages 20 to 25 it is second only to tuberculosis (Armstrong and Wheatley *Studies in Rheumatic Fever* Metropolitan Life Insurance Company Nov 1944) In New York City in 1938 there were 1 105 deaths reported from rheumatic fever and rheumatic heart disease as compared with a combined total of 247 from whooping cough meningitis measles diphtheria scarlet fever and poliomyelitis (see Figure 81)

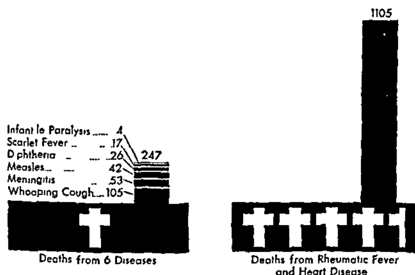


FIG 81 Deaths from rheumatic fever and heart disease compared with deaths from six other common infectious diseases New York City 1938 Data compiled by Dr Homer Swift (Kindness of Dr David I Rutstein and the American Public Health Association New York)

Already however either as the result of special efforts or because of an amelioration of the rheumatic infection itself or both or most likely of all because of considerable improvement in living conditions there is some indication that in the last three decades (1920 to 1950) there has been a slight but definite decline both in the severity and in the incidence of rheumatic heart disease (Hedley 1939 Wheatley 1949) evidences of which have been a drop from 27 cases per thousand patients in the wards of the Massachusetts General Hospital during the years from 1927 to 1930 to 22 cases per thousand during the years from 1937 to 1940 and finally 15 cases per thousand during the years from 1947 to 1950 a decrease from 26 cases per thousand at the Boston Floating Hospital in the years 1933 to 1937 to 9 per thousand from 1943 to 1947 and to 6 per thousand in 1948 and 1949 (kindness of Dr

James Baty) the complete clearing of a formerly long waiting list of children with rheumatic fever for admission to the House of the Good Samaritan in Boston, the decrease in rheumatic heart disease found recently in the school children of Denver Colorado and a drop of relative incidence of rheumatic heart disease among cardiac admissions to the John Sealy Hospital in Galveston from 7 6 per cent in the decade 1920–1929 to 2 1 per cent in the decade 1930–1939 (Decherd and Herrmann, 1943)

The broad term rheumatic heart disease includes acute subacute and chronic involvement of the heart of the 'rheumatic type (as discussed under the heading Pathology to follow) whether or not a clear cut history of rheumatic fever can be elicited The rheumatic infection itself is manifested by a widespread reaction of the tissues throughout the body in this respect resembling tuberculosis and syphilis on the one hand and allergy on the other In fact the terms rheumatic granulomatosis the rheumatic state and rheumaticosis have been suggested as better than the usual expressions rheumatic polyarthritis rheumatic fever, and the rheumatic infection (Fahr 1929 Coburn 1931 Graham 1932)

Etiology *Cause* The cause of the rheumatic infection that plays such havoc in the heart is not yet clear It is the subject of intensive research at the present time and the solution of the problem is awaited with the keenest interest. Streptococci of various types have been considered in some way responsible for many years and especially the hemolytic streptococcus (Coburn and others) the general consensus of opinion is that the Streptococcus hemolyticus is the chief exciting factor which precipitates the so-called rheumatic state throughout the body particularly in the heart Other exciting factors have however been noted such as typhoid vaccine (Bland and Jones 1935) and even injuries suggesting that the exciting factor is not specific nevertheless an acute streptococcus infection appears responsible in the vast majority of the cases The finding of streptococci or other bacteria in the blood joint fluid or pericardial or pleural fluid of acute rheumatic cases has been occasionally reported but is not considered of primary importance any more than the finding of immunologic reactions in tissues or blood A decade or two ago a virus origin of the disease was suggested but this has never been confirmed Whether the tissue reactions throughout the body are due directly to bacterial toxin or result indirectly from an intermediary agent or as an allergic response has not yet been settled Something akin to the last mentioned hypothesis with particular involvement of the body s collagen is at present thought to be most likely but much research on this problem is in progress

In recent years there have arisen interesting speculations concerning the possible role in the production of rheumatic fever of the action of hyaluronidase an enzyme on hyaluronic acid a mucopolysaccharide which with chondroitin sulfate is an important element in the ground substance of connective tissue synovial fluid and certain other parts of the body Certain strains of hemolytic streptococci produce hyaluronic acid and hyaluronidase and

salicylates have been reported to exert an antihyaluronidase effect The possible etiologic relationships suggested by these findings and by the effects of hormones (ACTH and cortisone) need much further study before definite conclusions can be established

Place of entry The place of entry of the rheumatic organism or virus (if such exists) into the body is probably the mouth The faucial tonsils have been considered to be the chief portal partly because their acute infection frequently ushers in acute rheumatic fever and partly because endocarditis may follow tonsillitis directly without any rheumatic symptoms However other lymphoid tissue in the pharynx and nose may also harbor the rheumatic or activating organism and the gastrointestinal tract and foci of infection in sinuses and middle ear have not been ruled out as possible sources of rheumatic heart disease

Rheumatic fever and chorea have been for many years regarded as the chief manifestations of the rheumatic infection that causes heart disease but tonsillitis growing pains and in very young children certain ill defined fevers or illnesses have been thought to be allied as lesser and somewhat uncertain evidences of the same infection The separation between these definite entities of rheumatic fever and chorea and the indefinite infections or symptoms mentioned and between the latter and distinctly nonrheumatic diseases is ill defined in our present state of knowledge the borderline must be regarded as very wide Thus the diagnosis of a rheumatic infection or of rheumatic endocarditis or heart disease still often remains a matter of opinion Two generations ago as now it was rather the custom to consider all infectious heart disease in young people that was not of syphilitic or of malignant bacterial nature to be rheumatic in origin One generation ago there arose the belief that septic infection of nonrheumatic type was frequently responsible when a rheumatic history was not obtainable Probably the truth rests somewhere between these views namely that the large majority of cases of infectious endocarditis are rheumatic in origin but that some arise from other infections particularly terminal in nature even when not of malignant bacterial type

The more carefully one investigates the past history of patients with the rheumatic type of chronic heart disease the more often one discovers a partly forgotten or mild rheumatism or chorea in such patients on the other hand a prejudicial view is inclined to interpret every tonsillar infection or muscle ache as rheumatic Furthermore rheumatic fever does not frankly appear as such in the first few years of life except in rare instances children affected with chronic endocarditis following some poorly defined illness in the second or third year of life are likely later to develop definite chorea or rheumatic fever with recurrent infection of the heart It is safest to regard and to treat as rheumatic all infectious heart disease of childhood (unless it is malignant bacterial endocarditis) even though occasionally the cause is not clearly the rheumatic infection the term rheumatic type of heart disease acute sub-

acute or chronic covers satisfactorily, for the present at least the cases of doubtful etiology

A definite history of rheumatic fever, mild or severe can on careful investigation be found in 60 to 70 per cent of cases with 'rheumatic heart disease and in another 5 to 10 per cent a history of chorea without rheumatism is obtainable Chorea alone with no evidence of infection is not so often followed by heart damage (Jones and Bland 1935) earlier opinions to the contrary were based on failure to exclude infection particularly rheumatic fever

Sex Rheumatic heart disease attacks both sexes, but statistical analysis usually shows a more frequent incidence among females in the ratio of about 4 to 3 or 5 to 4 In one group of 956 cases there were 525 females and 431 males (White and Jones 1928) and in another group of 1 000 cases studied at the House of the Good Samaritan in Boston there were 709 females and 291 males, a 7 to 3 ratio but the preponderance of beds available for females accounts partly for this high ratio (Jones and Bland 1942)

Age In communities where rheumatic heart disease is common it is found in the great majority of cases between the ages of 4 years and 50 years It rarely begins in the first four years of life and is especially rare before the age of two years A case of intrauterine rheumatic heart disease has however been reported (Kissane and Koons 1933) also a case in an infant aged only 17 months has been noted (Schwarz 1932)

Most recently a group of 26 very young children with active rheumatic fever has been reported by Logue and Hurst (1951) of these 26 10 were under the age of four there being 3 three years old 5 two years old and 2 one year old there were also 9 who were four years old in this group 6 who were five years old and 1 whose exact age at the onset of rheumatic fever was not known but who was under five years of age Despite such exceptions long experience has shown that as a rule rheumatic heart disease begins between the ages of 4 and 15 years with height of onset between the seventh and eighth years It has been found that about 1 to 2 per cent of the school children in parts of the United States and Canada where rheumatic fever is prevalent have rheumatic heart disease varying greatly however from place to place or from one part of a city to another (from less than 0 5 per cent up to 4 or 5 per cent) largely dependent on the degree of crowding of living conditions (Robey 1927 Keith and Pequegnat 1947 Quinn 1948) Although some cases develop relatively late that is after the twentieth year of life this is distinctly unusual The mortality beginning in the first decade increases steadily and is highest in the second and fourth decades when infections (especially recurrent rheumatism) and heart failure take their toll Occasional instances of survival to the age of 70 years and a few even to 80 or over (White and Bland 1941) are seen when the cardiac damage has not been extensive The prevalence of rheumatic heart disease (*chronic as well as acute*) by decades in the New England group of 956 cases already noted (White and Jones 1928) as compared with that of 684 cases analyzed 25 years later (White 1951) was as follows

Race All civilized races and nationalities appear susceptible to rheumatic heart disease although a somewhat lower incidence has been noted in China than in parts of Europe and America of the same latitude In New England people of English Scotch Irish Scandinavian French Polish Jewish German Italian and Negro stock have all been found with rheumatic heart disease

Table 6

AGE GROUPING OF CASES OF RHEUMATIC HEART DISEASE
IN NEW ENGLAND

Years	Group of 956 Cases Reported in 1928		Group of 684 Cases Reported in 1951	
	Cases	Percentage	Cases	Percentage
0–10	116	1[illegible].1	53	7.7
10–20	[illegible]99	31.3	2[illegible]3	3[illegible].6
20–30	135	14.1	71	10.4
30–40	165	17.3	91	13.3
40–50	1[illegible]3	1[illegible].9	102	14.9
50–60	78	8.2	89	13.0
60–70	35	3.6	38	5.6
Over 70	5	.5	17	2.5
Total	956		684	

Climate Climate appears to be an important factor in the incidence both of the rheumatic infection and of the rheumatic type of heart disease The colder wetter parts of the temperate zone particularly favor these conditions as do also the colder and wetter seasons of the year—winter and spring in New England autumn and winter in old England In the northern part of the United States the rheumatic infection and its permanent involvement of the heart are five times more frequent than in the southernmost part of the country or in the Philippine or Hawaiian Islands while in the midzone the incidence is between these two extremes For example in Boston at the Peter Bent Brigham Hospital the incidence of rheumatic fever in the years 1914 to 1923 was 1.85 per cent of all medical admissions the clinical incidence of mitral stenosis was 3.89 per cent and the incidence of mitral stenosis in the autopsy room was 4.68 per cent while in New Orleans at the Charity Hospital these percentages from 1916 to 1923 were 0.03 0.08 and 0.23 respectively and in Baltimore at the Johns Hopkins Hospital from 1914 to 1922 0.73 2.01 and 1.30 respectively (Harrison and Levine 1924) This climatic difference has been so great that victims of the rheumatic infection have been advised sometimes to move from northern latitudes to southern and a few have done so the reports from such a step have been in the main favorable (Coburn 1931 Jones White Roche Perdue and Ryan 1937) but it is to be noted that rheumatic heart disease has been discovered in recent years even in natives of tropical lands such as Cuba (Perez de los Reyes et al 1944) Puerto Rico (Francisco 1947) Panama (Hardgrove et al 1946) Curaçao (Hartz and Van der Sar 1946) and New Guinea (Levine 1946) Edstrom (1944) has even tried to influence the rheumatic infection by artificially producing a

tropical climate indoors in the temperate zone for long time treatment of active rheumatism with suggestive but not conclusive favorable results The Rocky Mountain states harbor a considerable amount of rheumatic heart disease up to 27 per cent of all cardiac patients (Cannon, 1946) as was confirmed by military experience during World War II while the high plateau and perhaps even the lower lands also in Mexico have shown a surprisingly great number of rheumatic heart cases some 30 to 50 per cent of all cardiacs (Chavez 1942 Cortes and Villarreal 1947) It is likely that both prevalence of hemolytic streptococcus infection and overcrowded living quarters play an important role in these areas

Family incidence One of the most interesting features of the rheumatic infection and of the rheumatic type of heart disease is their occurrence in different members of one family Several studies have indicated that from 3? to 50 per cent at least of patients with rheumatic fever, chorea or rheumatic heart disease have near relatives with a history of similar trouble (as compared to a control series) Three factors are probably responsible for such family incidence (1) inherited susceptibility to the rheumatic infection (2) close contact with the actual spread of the exciting organism from one throat to another and (3) crowded or unsanitary living conditions sometimes with inadequate food and clothing

Social and economic status An important factor in the occurrence of the rheumatic infection and of rheumatic heart disease appears to be the social and economic status of the individual These diseases are much more common by 100 per cent at least among the crowded poor than among the well-to-do inhabitants of almost every community In the large American private schools rheumatic fever chorea and rheumatic heart disease are infrequent while in the large public schools they are relatively common Crowding exposure to cold and wet without sufficient protection malnutrition and fatigue are probably all factors in producing this contrast

Epidemic form Finally there is some evidence that at times under suitable conditions the rheumatic infection in the nature of rheumatic fever assumes an epidemic form This was noted among the soldiers during World War I and infrequently among civilians since and was encountered again in World War II It may occur when an infecting organism of unusual virulence attacks a group of susceptible individuals exposed to adverse conditions such as bad weather and fatigue It has been especially noted in groups of young people immediately following infection by a virulent hemolytic streptococcus in epidemic form a certain number of susceptible individuals though a small percentage of the persons attacked by the original infection may develop rheumatic fever In camp barracks and other living quarters of military personnel during World War II about 4 to 5 per cent of the young men exposed to and infected by the hemolytic streptococcus of various strains developed rheumatic fever some 10 to 15 days later this was especially noted among the new recruits and in more crowded living conditions and in colder climates (Feasby 1944 and Barber 1946)

Pathology A generation ago endocarditis was the only well recognized common manifestation of rheumatic heart disease acute or chronic pericarditis was admitted as an occasional complication but little attention was paid to involvement of the myocardium or as a matter of fact to the widespread effects of the disease throughout the body Much advance in the proper understanding of this kind of heart disease has come in the last thirty years

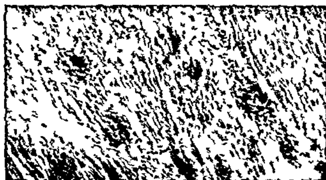
The more severe the rheumatic infection in early youth the more extensive as a rule is the cardiac damage Once it was thought that only about two thirds of the attacks of rheumatic fever and about one third of those of chorea affected the heart but careful examination is now revealing a somewhat different incidence There was for example evidence of permanent cardiac damage in 86 per cent of 518 cases of rheumatic fever in 73 per cent of 348 cases of chorea and rheumatic fever and in 3 per cent of 134 cases of uncomplicated chorea analyzed at the House of the Good Samaritan in Boston (Jones and Bland 1935) Findings vary however as indicated by another series of 175 cases of acute rheumatic fever 50 per cent of whom showed no evidence of heart disease after follow up periods averaging seven years (Brown and Wolff 1940) Electrocardiographic and postmortem examinations have often shown myocardial and even slight endocardial involvement even though on physical examination there had been no sign whatsoever of heart disease It is probable that in every case of rheumatic infection there is some heart disease however slight or transient and that in a certain percentage of the total number there is complete recovery with return to normal or at least not sufficient deformity of valves or lesion of myocardium or pericardium to produce abnormal signs

The typical heart lesion of the rheumatic infection is an inflammatory reaction about the smaller arteries consisting of groups of small round mononuclear cells with a few giant cells (Aschoff 1904) this has been called the Aschoff body (Figure 82) and its discovery anywhere in the heart or pericardium has been considered almost pathognomonic of the activity of the rheumatic infection There may be but few of such lesions present or they may be widespread and in groups They apparently come and go leaving no trace unless the disease has been so extensive that nutrition has been interfered with and scar tissue results a sequela of more than slight fibrosis is very rare in the myocardium although a few instances have been recorded of rheumatic heart block remaining as a chronic state after it has appeared during the acute rheumatic infection

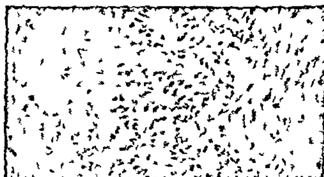
Aschoff L Zur Myocarditisfrage *Verhandl d deutsch path Gesellschaft* 1904 VIII 46

Aschoff here gives the first clear description of the more or less specific rheumatic myocardial lesion which has been called by his name (Aschoff body) (The translation is by myself)

We have succeeded in establishing the histological structure of the myocardial reaction to the rheumatic infection by finding peculiar nodules which appear to be specific These nodules were indeed clearly defined in only two cases of recurrent endocarditis but in other cases cellular proliferations corresponded exactly in



A



B



C

FIG 82 Rheumatic myocarditis (*A*) Microphotograph showing typical Aschoff bodies in the (ventricular) heart muscle in acute rheumatic heart disease (Thalhimer and Rothschild *J Exper Med* 1914 XIX 417)

(*B*) Microphotograph (higher power) of myocardium of child dying of severe rheumatic infection showing extensive destruction of the muscle cells with invasion by leukocytes and a few multinucleated giant cells (Kindness of the House of the Good Samaritan Boston)

(*C*) Microphotograph of myocardium from case dying of severe recurrent rheumatism There is evident at the left old fibrotic change from a previous rheumatic infection, and at the right new necrotic and hemorrhagic lesions due to the recurrent rheumatism. (Kindness of the House of the Good Samaritan Boston)

their locations to the lesions of these two hearts They were regularly situated in the neighborhood of the small and medium sized blood vessels and often showed the closest relationship to the adventitia of these vessels There even was found a disease of all the vessel walls somewhat comparable to that described for arteritis nodosa The above mentioned nodules are extraordinarily small highly submiliary and are comprised of collections of unusually large cells with one or more abnormally large slightly notched or polymorphic nuclei The grouping of cells often occurs in the form of a fan or a rosette The periphery of the nodule is composed of the large nucleated cells and the center often of an apparently weakly staining necrotic mass of coalescent cellular protoplasm With careful observation the fan shaped foci remind one of the smallest necrotic areas with cellular periphery which one finds so often in gouty kidneys In the rheumatic nodules one has to do not with the tubercular or foreign body giant cells with several regularly formed nuclei but with structures which resemble rather the large nucleated cells in certain sarcomas or in pseudoleukemic proliferations On the other hand the nodules are not composed solely of such large nucleated cells but small and large lymphocytes and also polymorphonuclear leukocytes are wedged in between the large cells at least at the periphery or else themselves comprise an outer zone from which irregular stray cells extend out further into the connective tissue interspaces In these outer areas there can still be found single large nucleated cells and all gradations down to simple large leukocytic elements which are more or less commonly found in the neighborhood of the smallest vessels in all inflammatory reactions These leukocytic elements are the large cells which Hayem and Romberg have described but whose origin remained doubtful in their minds Out of these large cells which are the adventitial cells of the blood vessels swollen by inflammatory reaction the large nucleated giant like cells are formed which single or collected in nodules give to the rheumatic proliferations a characteristic stamp It should further be observed that the number of eosinophilic cells in these nodules is very small

Years later it was demonstrated that the Aschoff body is not the earliest tissue change in the rheumatic infection but often is a rather late reaction probably a part of the process of recovery and repair (Coburn 1933) The earliest tissue changes are those of destruction (necrosis) and a tendency to hemorrhage throughout the body especially well marked in the more severe cases The myocardium particularly is involved and may be so seriously damaged in the sicker children that the heart dilates acutely or subacutely Such dilatation of the heart may lead to death from heart failure or to more or less permanent cardiac enlargement or it may be followed by good recovery with more or less complete return of the heart to normal size The recognition of this fact is of the greatest importance in the proper understanding of the cardiac symptoms and signs in the course of the acute and subacute rheumatic infection in the analysis of the late after-effects and in rational prognosis and treatment

The typical rheumatic endocarditis consists of a so-called verrucous inflammatory reaction tiny vegetations of thrombotic nature composed chiefly of fibrin and tending particularly to appear in a row on the atrial surface of the mitral and tricuspid valve cusps and on the ventricular surface of the semilunar valve cusps (Figure 83) at the line of closure not at the edge although

sometimes they are distributed elsewhere over the cusps The exact pathogenesis of these thrombi or of the damaged areas of the endocardium on which the thrombus formation takes place is not known whether due to direct toxic action of the blood stream or via the blood vessels in the valves or to local allergic reaction to agent or agents in the blood (manufactured elsewhere) In any event the slight trauma caused by valve closure appears of some importance in favoring the appearance of the earliest lesions In fact nonrheumatic



FIG 83 Photograph showing acute and chronic rheumatic endocarditis of the aortic valve Note the vegetations along the line of closure adhesions of the cusps to produce slight aortic stenosis scarring of the endocardium below the valve and thickening of the chordae tendineae of the mitral valve The patient was a boy 14 years old (Kindness of Dr Ronald Grant Guy s Hospital London)

bland thrombi of small size very probably are deposited on the lines of closure of the heart valves especially the mitral on occasion almost as a normal event the result of a variety of influences they may do no serious harm but can quite likely result in a slight chronic thickening of the valve edge which may justifiably or not arouse suspicion of a rheumatic etiology Besides the involvement of valve cusps there is commonly in rheumatic endocarditis especially of the severe type inflammation of the chordae tendineae and of the wall of ventricle or atrium especially of the left atrium just above the valve this results in scarring and in the case of the chordae in thickening shortening and coalescence to add to the valve deformity

Rheumatic pericarditis consists of a fibrinous or a serofibrinous reaction more or less extensive sometimes giving rise to the typical bread and butter appearance (as shown in Figure 134 page 710) but rarely to large effusions (a typical serous exudate rarely bloody) In healing small or large scars are left with or without localized or complete adhesions and only rarely with any important external adhesions Constrictive pericarditis of sufficient degree to cause symptoms or signs (Pick s disease) has not been encountered once in 1 000 cases of the rheumatic infection many with pericarditis followed over a ten to twenty year period at the House of the Good Samaritan in Boston (Jones and Bland 1942) nor has any one of 53 cases of chronic constrictive pericarditis examined by myself had a rheumatic etiology although two among them had coincidental rheumatic valvular disease

When as frequently happens myocardium endocardium and pericardium are all involved we speak of *pancarditis* and now and then especially in young children such pancarditis may be very severe and overwhelming resulting in early death from heart failure

Furthermore the rheumatic infection may attack other organs beside the heart, pericardium joints and brain (chorea) The arteries—aorta pulmonary artery and smaller visceral and peripheral vessels—the lungs the pleurae the diaphragm and the peritoneum may be involved by hemorrhages or by lesions resembling the Aschoff body sometimes with serious consequences An important and interesting pulmonary rheumatic lesion in severe cases is the hemorrhagic consolidation sometimes labeled erroneously rheumatic pneumonia this lesion quickly comes and goes

The rheumatic infection is typically a slow one and recurrent a fresh invasion of the heart is common on top of healed lesions of valves or of atrial or ventricular endocardium of chordae tendineae or of pericardium

The infection may clear up in some cases as stated above with little or no trace but commonly a scarring of the endocardium is made evident by valvular deformity Chronic pericardial damage sometimes persists in the nature of adhesions of varying extent and importance Rarely there is a residual myocardial lesion as shown by permanent heart block or ventricular dilatation A discussion of the particular valve lesions of pericarditis and of heart block will be found in Parts III and IV of this book Suffice it to say here that there is a very wide variation of cardiac damage resulting from the rheumatic infec

tion and constituting chronic rheumatic heart disease not only with respect to the particular parts of the heart involved but also with respect to the degree of involvement

It should be added that chronic cardiac dilatation accompanying valvular defects or pericardial adhesions may be due as much or more to the rheumatic infection of the myocardium as to the particular valvular handicaps that cause heart strain Indeed it may be conjectured that in rare cases cardiac enlargement even of high degree and leading to failure may be due to an old severe antecedent rheumatic involvement of the myocardium with little or no endocardial or pericardial scarring This is an explanation of some of the cases of heart disease of unknown origin which appeals to one as logical but which as yet lacks proof

Symptoms The symptoms of rheumatic heart disease depend upon three factors (1) activity of the rheumatic infection (2) obstruction to the circulation resulting from the specific lesions and (3) heart failure which may come as the result of overwhelming acute or subacute myocarditis or of chronic valvular disease or of disturbed heart rhythm or of two or even all three of these conditions combined Many persons with chronic rheumatic heart disease have no symptoms at all and live active lives without difficulty Of greater immediate importance than study of the structural defects is the determination of the presence or absence of activity of the rheumatic infection

The symptoms of acute or subacute rheumatic infection include those of any infection but depend also on the reaction of the individual patient to the causative agent Joint pain tenderness swelling heat and redness muscle aching chorea (rarely combined with joint symptoms) fever chills (rarely) sweating (sometimes profuse) weakness effort syndrome malaise anorexia epistaxis (occasionally), and loss of color and weight are all symptoms of the active rheumatic infection Their severity varies with the virulence of the infection and the resistance of the patient They may be mild and hardly noticeable —merely slight fever and malaise with or without muscle or joint soreness—and not always sufficient to cause the victim to stop school or work or to induce the family to consult a physician unless they have been educated by previous experience or are aware of the likelihood of involvement of the heart In rare cases of rheumatic fever there may be abdominal pain simulating that of or actually due to an acute appendicitis A low grade rheumatic heart infection ordinarily called subacute rheumatic carditis may set in and last for weeks or months or even years especially in children showing itself only by a loss of energy and by the appearance of ill health and of a slight elevation of temperature at intervals or daily (99° F or a little more by mouth or 100° F by rectum) Such a situation is very common while a virulent polyarthritis in children is relatively rare A severe short attack of rheumatic fever with extreme joint involvement and little or no heart disease is much more likely to occur in the adult Years ago it was a common though by no means invariable rule that the older the individual the more the joints suffered and the less the heart the younger the subject the more the heart suffered and

the less the joints In recent years on the other hand a fulminating polyarticular rheumatism is rarely seen at any age even in New England this is apparently due to a spontaneous change in the virulence or character of the rheumatic infection itself though the common and early use of the salicylates (especially aspirin) for any illness by the populace at large may also have a modifying and misleading influence on the acute rheumatic process

The heart itself when acutely invaded by the rheumatic infection only occasionally causes symptoms Sometimes it may ache so that precordial discomfort is felt sometimes there are sharp pains in the chest although they are not common rarely there is actual angina pectoris occurring usually in subacute or chronic valvular disease with marked aortic regurgitation probably dependent on insufficient coronary blood supply due not only to low diastolic blood pressure but also to a storm of vasoconstriction involving the coronary arteries and producing transient hypertension in a sensitive individual Infrequently disturbances of rhythm occur such as premature beats or paroxysmal tachycardia giving rise to palpitation usually the palpitation that may be felt is but a part of the effort syndrome that accompanies any infection Dyspnea also is usually due to effort syndrome but sometimes it arises from an acute pericarditis or from cardiac dilatation and failure accompanying an overwhelming acute myocarditis When the heart fails during the acute rheumatic infection in childhood it is a total heart failure with little or no dyspnea but with congestion behind the right ventricle giving rise on occasion to upper abdominal discomfort from engorgement of liver and other abdominal viscera

The chronic rheumatic heart frequently fails from the strain of valvular disease complicated by a disturbing arrhythmia (especially atrial fibrillation) or by an acute infection (rheumatic or nonrheumatic) then appear the typical symptoms of congestive failure (see Chapter 30) Angina pectoris may occur with marked aortic stenosis or regurgitation but rarely with other valve defect Also without actual failure the obstruction due to mitral stenosis may occasion congestion of the lungs with dyspnea cough hemoptysis or it may rarely cause hoarseness from laryngeal paralysis At times the obstruction due to tricuspid stenosis may block the return of blood into the right ventricle and left heart chambers with resulting congestion of liver and large veins similar to the condition found in cases of chronic constrictive pericarditis (so-called Pick s disease)

The symptoms of an active rheumatic infection may frequently be superimposed on those of chronic rheumatic heart disease when there is a recurrent rheumatic attack in fact heart failure in chronic rheumatic heart disease is often precipitated by the new infection or is due more to its presence than to the old lesion

Signs The signs of rheumatic heart disease are dependent on the factors of activity of the infection of the strength of the heart and of the particular lesions There may be nothing but slight enlargement of the heart with a systolic murmur at the apex or a slight diastolic murmur along the left border

of the sternum found on routine examination there may be an enormously enlarged heart with several murmurs absolute arrhythmia and marked congestive failure or there may be any combination of signs between these two extremes Commonly in the child there is slight to moderate cardiac enlargement with normal rhythm moderate systolic and middiastolic murmurs at the apex (the result of left ventricular dilatation during the course of the first rheumatic infection and later on, of mitral valve disease itself) and sometimes a diastolic blow (of aortic regurgitation) along the left border of the sternum without frank congestive heart failure but frequently with slight fever due to activity of the rheumatic infection It is a common experience to note the disappearance of the physical signs of rheumatic heart disease (enlargement, systolic murmur and even mitral diastolic murmur) when cardiac dilatation subsides along with the active rheumatic infection (Bland Jones and White 1936) these signs especially the mitral diastolic murmur used to be attributed to chronic heart disease but now it is realized that usually an interval of several years is necessary for the establishment of structural mitral stenosis Commonly in the adult on the other hand especially in the female there is a well marked apical diastolic murmur of mitral stenosis, absolute arrhythmia of atrial fibrillation and very limited cardiac reserve or slight to moderate congestive failure with or without aortic regurgitation in the adult male one finds somewhat more often a preponderant or even seemingly isolated aortic valve lesion (stenosis, regurgitation or both) with normal rhythm Although these findings are the most common they may be replaced by others The signs of the particular valve defects will be discussed in Part III

The *more severe cases of active rheumatic infection may show* also frank congestive heart failure which in childhood involves the whole heart with resultant systemic venous congestion (big liver and dependent edema including the face with the child lying flat) rather than pulmonary congestion due to primary left heart failure (Walsh and Sprague 1941)

Infrequently one finds in acute rheumatism two additional signs which are subcutaneous and cutaneous manifestations rheumatic nodules and skin lesions

Rheumatic nodules are important signs of a severe rheumatic infection their presence indicates that the infection is still active even though they persist or recur for many months These nodules vary in size number location and with the severity of the disease Usually of pinhead to pea size and shape rarely as large as Lima beans they are found most commonly subcutaneously and are loosely attached to tendon sheath periosteum or joint capsule over elbows knees ankles skull fingers wrists toes and shoulders in frequency in about the order named and usually more or less symmetrically on the two sides of the body (Figure 84) When very extensive they may be found scattered over the entire head thorax and long bones In number they vary from two or three a common finding to one hundred or more very rarely *They tend to come and go singly or in crops* each one lasting for a few days or weeks they may not completely disappear for months In some parts of the

world they are more common than in others but this variation is probably due mainly to the severity of the infection Their incidence has extended from 2 or 3 per cent to over 75 per cent in different groups of patients with acute rheumatic infections in different communities They are less commonly seen nowadays in New England than they were two or three decades ago perhaps paralleling the decrease in the severity of the disease itself

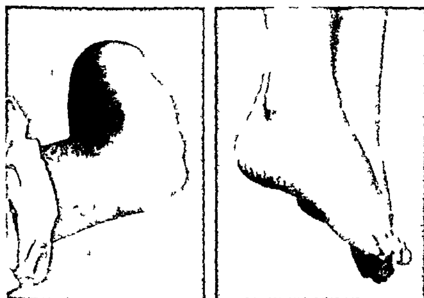


FIG 84 Photograph showing joints of child with rheumatic nodules on elbow ankle and foot Note nodule also on the tendo Achillis (Kindness of the Cardiac Clinic Children's Hospital Boston)

Erythema multiforme (marginatum) is the commonest of the cutaneous signs accompanying the rheumatic infection occurring in about 15 per cent of the cases at some time or other tending to recur over periods of a few weeks or months and to appear in patients who have had or who later develop rheumatic nodules Erythema nodosum urticaria and angioneurotic edema are relatively rare Purpura rheumatica and petechial hemorrhages are sometimes found Petechiae may be readily produced in the skin of subjects with an acute or subacute rheumatic infection by pressure as with a blood pressure cuff this is due to the tendency to bleed which is a part of rheumatic fever as well as of bacterial endocarditis

Other occasional signs of severe rheumatic infection are those of acute pleuritis acute pericarditis or both fibrinous or with effusion and sometimes hemorrhagic pulmonary disease (areas of hemorrhagic consolidation) which are apparently of rheumatic origin and as a rule rapid in their appearance and disappearance Chronic adhesive pericarditis may show itself in the recovered cases but often it gives no clear sign This will be further discussed in Part III of this book

The results of all other methods of examination of an individual with rheumatic heart disease are likewise dependent on the three factors of activity of infection cardiac insufficiency, and the particular structural lesion Commonly it is the presence of mitral valve disease and of stenosis of that valve that accounts for the findings in chronic cases

The blood pressure is normal or low unless there is a complicating essential hypertension thyrotoxicosis, or considerable aortic regurgitation The pulse and pulse pressure are very full when there is marked aortic regurgitation small when there is considerable mitral stenosis and very small when there is pronounced aortic stenosis

Roentgenologic study is of help in following a case of rheumatic heart disease In the acute infection and early stages of organic involvement the heart shadow may be normal or it may reveal enlargement and change in shape of the heart shadow due most often to more or less acute dilatation of the heart (Figure 85) or less commonly to accumulation of fluid in the pericardium in rheumatic pericarditis or to both of these conditions In chronic cases it shows various typical changes of shape and size when there are well marked chronic valvular lesions (see Chapter 26)

The electrocardiogram may be normal in rheumatic heart disease except for a rapid rate (sinoatrial tachycardia) which is found frequently, but if many serial records are taken of any case abnormalities are commonly found though often in but a few records When the electrocardiogram is abnormal it may show either an arrhythmia delay in conduction between atria and ventricles abnormal *T* waves intraventricular block or abnormal axis deviation The rhythm is absolutely irregular in more than half of the adult cases with marked mitral stenosis but it is generally normal or disturbed only by premature beats in aortic valve disease, pericarditis or preponderant mitral regurgitation Slight grades of heart block as shown by *P-R* intervals of 0 21 or 0 22 second are common during the acute rheumatic infection (Figure 86) and even *P R* interval prolongation to 0 25 second dropped beats or higher grades of block are occasionally seen This finding of block may be the only sign of cardiac involvement and it has been noted in rare cases as the first evidence of the rheumatic infection in the body polyarthritis developing shortly afterward (White 1916) Also in very rare cases the heart block during the active infection may progress to such a high degree that Adams Stokes attacks occur for a short time As a rule the heart block clears up when the rheumatic infection subsides but a few instances of permanent rheumatic heart block have been noted and it has also been observed that rheumatic heart cases with a persistently prolonged *P-R* interval are more likely to develop atrial fibrillation than are those whose *P R* interval is normal due in part it is suggested to vagal action (Bruenn 1937 Altschule 1939) It is important to note moreover that prolongation and variability of the *P R* interval can occur in normal children as well as in rheumatic children without evidence of rheumatic activity (Reyersbach and Kuttner 1940)



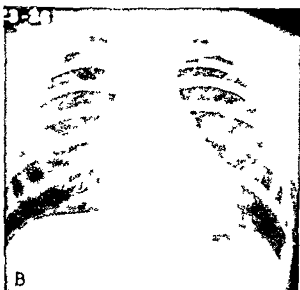


FIG 85 Roentgenograms showing (*A*) considerable dilatation of the heart in a young girl during acute rheumatic fever and (*B*) reduction in heart size several months later after complete subsidence of the infection At the time the first record was taken there were systolic and middiastolic murmurs at the apex which disappeared wh n the dilatation subsided *There was no evidence of acute pericarditis Note the rather localized* pulmonary edema in the right lung in (*A*) The transverse diameter of the heart in (*A*) was 11 6 cm and in (*B*) 10 4 cm

In addition to the delay in atrioventricular conduction slight deformities of the *QRS* and *T* waves or of the *S-T* segment are occasionally noted during the acute and subacute infection and may represent slight transient intra ventricular block myocarditis and pericarditis, rarely they may persist In a few cases of chronic rheumatic heart disease particularly with mitral stenosis bundle branch block of the right type with wide S_1 or QS_1 may be

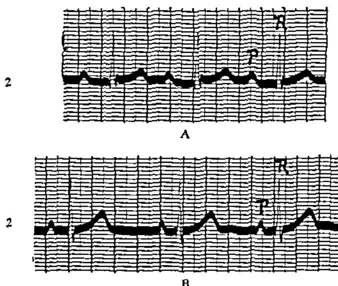


FIG 86 Electrocardiograms showing Lead 2 in (*A*) during acute rheumatic fever Dec 17 1935 and in (*B*) two weeks later during convalescence Jan 2 1936 Note the prolonged *P R* interval (0 25 second) in (*A*) and normal *P R* interval (0 17 second) in (*B*) Boy 13 years old Time = 0 1 and 0 2 second

found Finally it is common to find abnormal axis deviation and ventricular preponderance in chronic valvular disease if either mitral stenosis or aortic regurgitation is preponderant and of marked degree right axis deviation occurring with the former and left axis deviation with the latter Absence of abnormal axis deviation by no means rules out either valvular lesion in fact high degrees of both may be present in the same case with normal electric axis deviation the effect of involvement of one of the valves neutralizing the effect of involvement of the other in the classical limb leads but the precordial leads *reveal the enlargement of both ventricles A very interesting* electrocardiographic finding occasionally seen in acute rheumatic fever with congestive heart failure is a shift of the electric axis to the right due doubtless in large part to the acute right ventricular dilatation (more marked than that on the left side) which decreases or disappears with the patient s improvement or recovery (Walsh and Sprague 1941) Prolongation of the *Q T* time has been reported in rheumatic fever but it is not a consistent finding and may be due to other factors (e g cardiac enlargement) rather than to the rheumatic fever itself

Blood and urine are frequently abnormal when there is an active rheumatic or complicating infection or congestive failure A leukocytosis of 10 000 or over often but not always accompanies acute rheumatic heart disease the severer the infection the higher the white count but it rarely passes 20 000 A slight or even moderately severe hypochromic anemia is common in children with active rheumatic heart disease The sedimentation rate of the blood is usually increased in proportion to the activity of the rheumatic disease and may be the only evidence that persists of a long-drawn out low grade infection The blood culture is usually negative A positive skin re action has been reported as a frequent finding when the toxic filtrate of the hemolytic streptococcus (or its nucleoprotein) is injected intradermally in patients who have had rheumatic fever but this has been found to be a non specific reaction that is it occurs also in cases who have had Streptococcus hemolyticus infections without rheumatic fever Albuminuria is the usual finding during congestive heart failure and during moderate or high fever in the acute rheumatic infection Occasional red blood corpuscles are frequently found in the urinary sediment during the active infection

Course and prognosis Rheumatic heart disease begins with an acute in vasion of the heart generally in childhood between the ages of 4 and 12 years Instances of very early infection are on record even in the fetus and in the nursing infant whose mothers had rheumatic fever at the time on the other hand the rheumatic infection and resulting heart disease have sometimes occurred first in adult life initial attacks of rheumatic fever have been reported in six patients over 60 years of age (Ferris and Myers 1935) I have myself encountered cases with recurrent attacks at 66 and at 72 years of age The earlier in life the cardiac involvement the more serious it is likely to be and the shorter the patient s life It is usual for the child to survive the first rheumatic infection whether it is frank rheumatic fever chorea ill-defined sickness or rheumatic heart infection alone Although this earliest infection is often mild it may last for months or years and leave a badly crippled heart Recurrent infections throughout childhood may cause death by heart failure by the toxic effect of the disease itself or by complications But usually there is survival in spite of one two three or more fresh attacks or exacerbations of rheumatism in childhood and youth the victim showing a variable amount of permanent heart damage by the time he reaches the age of 20 years Rarely does he escape unscathed unless he has had but one or at most two slight attacks of rheumatism The greater the number of recurrences of the infection the greater is the heart damage In adult life he runs far less risk from new rheumatic attacks but on the other hand he runs three other risks (1) atrial fibrillation (2) congestive heart failure and (3) subacute bacterial (Streptococcus viridans) endocarditis The first of these complications (atrial fibrillation) is common in the case of well marked mitral stenosis but it is relatively rare in all other cases The second (congestive failure) is likely to occur in any severely damaged heart when there is aortic or mitral valve disease uncontrolled tachycardia (especially in atrial fibrillation)

infection rheumatic or otherwise which adds appreciably to the strain The third (subacute bacterial endocarditis) is commonest in aortic valve disease or with mitral lesions in which stenosis is not marked that is when regurgitation predominates so it is most common in just that type of chronic rheumatic heart disease which atrial fibrillation and congestive failure are not likely to accompany but why this should be so we do not yet know

Death from heart failure or complicating infection commonly overtakes the victim of rheumatic heart disease in the second fourth or fifth decade of life after many years usually ten to twenty of partial crippling and restriction of activity and after a few years usually two to five of partial or complete invalidism Sometimes however if the lesions are but slight and the subject is careful fortunate or both he may survive to old age and die a noncardiac death Slight mitral stenosis or regurgitation slight aortic stenosis or regurgitation and a noncrippling adhesive pericarditis are all lesions that are well borne with respect both to duration and to activity of life but in general the mitral valve lesions are better borne than the aortic A ten year follow up of 506 cases with rheumatic valvular lesions gave a relative mortality of 3 7 per cent for mitral insufficiency, 12 5 per cent for mitral stenosis and 37 4 per cent for aortic valve lesions with or without mitral valve involvement (Svartz and Ernberg 1947) In Texas Fashena (1944) found the death rate from rheumatic fever in the school age period to be not very different from that in New England or in the United States as a whole Cases of mitral stenosis surviving the age of 80 years are now on record (White and Bland 1941) Wilson and Lubschez (1948) have presented some interesting data as to longevity based on a thirty year period of observation of 1 042 children who had rheumatic fever The mean age at onset of their rheumatism was 6 5 years The average length of observation was 14 8 years among 226 deaths 75 7 per cent were due to rheumatic disease of the heart and 10 2 per cent to subacute bacterial endocarditis They concluded that an affected child has 4 chances out of 5 to survive childhood 3 out of 4 to survive puberty and then 19 chances out of 20 to survive early adult life, with an overall chance of 1 out of 2 to survive the age of 40 years

Complications The three most important complications of rheumatic heart disease have been mentioned above (1) atrial fibrillation which complicates two thirds of the cases of considerable mitral stenosis and about one fifth of all cases of chronic rheumatic heart disease (17 5 per cent of the 956 cases of White and Jones series) (2) congestive heart failure which eventually complicates at least two thirds of all cases and (3) subacute bacterial (*Streptococcus viridans*) endocarditis which attacks one in every 4 to 20 cases (25 to 5 per cent) of rheumatic heart involvement Jones and Bland (1942) have found subacute bacterial endocarditis in 16 (7 9 per cent) of 203 fatal cases of rheumatic fever or rheumatic heart disease while Gelfman (1943) has reported the finding of such involvement in 25 [illegible] cent of autopsied cases of rheumatic heart disease in two Boston hosp[illegible] common or important complications are co[illegible] disease [illegible] of White and Jones

series) essential hypertension (also in 2 per cent of White and Jones series) syphilitic aortitis congenital defects thyrotoxicosis and emphysema (each of which last named conditions complicated less than 1 per cent of White and Jones series) Neurocirculatory asthenia frequently is found in varying degree in the victim of rheumatic heart disease it was well marked in 37 of the 956 cases (4 per cent) of the series noted above (White and Jones) Mild and serious infections of all sorts nephritis pulmonary disease nervous diseases and lesions of the gastrointestinal tract may complicate rheumatic heart disease but it is of interest to note that glomerulonephritis rarely accompanies rheumatic fever itself (Baehr and Schifrin 1931) The relative infrequency of pulmonary tuberculosis in cases of well marked mitral stenosis has been pointed out it has been suggested that the chronic pulmonary stasis in mitral stenosis protects the lungs from tuberculosis

Four complications of rheumatic heart disease are largely dependent on the mitral stenosis or congestive failure that may be present The commonest is pulmonary embolism which may arise in dilated right heart chambers but most often comes from thrombosed veins in legs resulting largely from the venous stasis secondary to the heart trouble Embolism to brain or elsewhere may result from thrombosis in the left atrium Acute pulmonary congestion producing edema or hemoptysis may come from increased pressure in the pulmonary circulation due to mitral stenosis especially when there is a rapid heart rate Rarely hoarseness may result from left recurrent laryngeal paralysis

Another rare complication namely that of angina pectoris may attend rheumatic heart disease it was found in 13 of White and Jones series of 956 cases the 5 older cases having coronary disease and the 8 younger ones marked aortic regurgitation Angina pectoris may also very rarely complicate mitral stenosis in young people (Hochrein 1930)

Of disturbances of rhythm atrial fibrillation and heart block have been discussed Atrial flutter is rare generally complicating mitral stenosis Paroxysmal tachycardia (regular) is common but less frequent than atrial fibrillation The presence of sinus arrhythmia although somewhat favorable is of little aid in the judgment of a case since it does not indicate that the heart is normal and since it does not prove that a low grade active infection is no longer in progress as was once thought

Treatment No treatment for rheumatic heart disease per se is needed unless one or more of the important complications are present—infection atrial fibrillation or flutter or congestive failure The treatment of the arrhythmias and of congestive failure is discussed in Part IV of this book In prevention of acute rheumatism either in first or in recurrent attacks the most important measure is the avoidance of upper respiratory infections or the early and adequate use of penicillin if the hemolytic streptococcus is the offending agent Although helpful it is not essential to enlist the aid of a mild climate for children have been kept well even in open air sanatoria in the north in the winter by practical exclusion of infected contacts (Hubbard and Griffin 1940)

If acute or subacute rheumatic infection is present *rest in bed,* a light simple diet with adequate vitamins and appropriate therapy directed against the infection are indicated Usually *good nursing care* is of prime importance and worth more than most drugs Satisfactory gain in weight is a good indication of the favorable progress of convalescence but it is not a sign of cure

In the third edition of this book it was stated that for the rheumatic infection itself no specific therapy has as yet been established although much reliance has been placed by some on the *salicylates* which without any question have a well nigh specific effect in the rapid control of fever joint swelling and pain in rheumatic fever for which purpose they may be freely used It is possible also though not proved that salicylate therapy may help to effect a rapid absorption of rheumatic pericardial and pleural exudate and effusion ' Since that time hormone therapy of arthritis and certain other diseases including rheumatic fever, has been introduced which may or may not prove to be specific or very near it

Hormone therapy The application of ACTH (adrenocorticotropic hormone) to acute rheumatic fever has been tried recently with surprising immediate success in the majority of cases for example seven patients at the House of the Good Samaritan in Boston given 10 to 25 mg of ACTH four times a day for four to six weeks have all responded favorably As a rule their temperature has been reduced to normal in two to three days their sedimentation rates have become normal in two weeks and even those seriously ill with congestive failure have improved greatly although they still may need other treatment for the congestion itself Cortisone also has been found to be effective in suppressing the disease (Hench et al, 1950) These preliminary observations of course need further confirmation and more prolonged follow up

Salicylate therapy A dose of 15 to 30 gr (1 to 2 gm) of sodium salicylate with an equal amount of sodium bicarbonate every two to four hours until relief of symptoms and of fever or a toxic reaction (tinnitus nausea vomiting urticaria) has ensued is sometimes recommended with great benefit in this way even 150 to 240 gr (10 to 16 gm) may be administered in a single day Rarely is it necessary or possible to continue such a large dosage for more than a few days For children the dosage of salicylate may be halved and for infants one fifth to one tenth of the amount given to adults should suffice but of course this medicine will rarely be needed at such an early age

Intravenous salicylate therapy in large dosage has been tried out controlled by testing the concentration of the drug in the blood (Coburn, 1944), but its early promise like the saturation by oral salicylates a good many years ago has not been confirmed Thus the statements made in the previous editions of this book still hold namely that the antipyretic effect of salicylates if constantly given may conceivably be harmful by masking some of the evidences of activity of the infection and so misleading one into a false sense of security and that if salicylates are used they should be employed only for symptoms of discomfort due to exudative reactions to the disease and occasionally

omitted for a few days at a time to determine the true course of the disease (temperature leukocyte count and signs and symptoms) However in the course of the trial of intravenous salicylate therapy a useful test for blood salicylate content was devised It has been demonstrated incidentally that as high a blood concentration of salicylate can be secured by oral administration as by intravenous Finally a warning is due as to the toxic effects of salicylate poisoning including a tendency to bleed and even delirium—such toxicity is more readily produced by intravenous administration

Vitamin C therapy Apparently midway between the effects of ACTH and salicylates is that of massive doses of vitamin C the favorable effect of which has recently been described by Massell et al 1950 Acute rheumatic involvement has been controlled in a series of cases by the administration of 1 gm of vitamin C in orange or apple juice four times a day The exact mechanism by which this effect is produced is still obscure

No place has been found for antihistaminic drug therapy in rheumatic fever despite the common supposition that this disease may be related to the allergies

Serum treatment of the acute rheumatic infection whether or not the infection involves the heart has never evolved from the experimental stage The use of specific monovalent or polyvalent streptococcus vaccines has also been suggested and tried but further study is needed before definite conclusions can be reached A possible success of such therapy is to be ascribed rather to the reduction of streptococcus infections which may excite the rheumatic infection than to the primary control of the rheumatic infection itself

A much more important prophylactic measure recently introduced that bids fair to reduce the incidence of the rheumatic infection in initial and especially in recurrent attacks has been first the administration of sulfonamide drugs in small dosage routinely throughout the winter and spring to susceptible children (e g 1 0 to 1 3 gm 15 to 20 gr sulfanilamide divided into 2 or 3 doses daily to a child of 8 years) to ward off or in larger dosage to treat the hemolytic streptococcus infections that so often precipitate active rheumatism and heart disease (Thomas et al 1939 1941 1942 Coburn 1941 Hansen et al 1942 and Kuttner and Reyersbach 1943) and more promising still of late the use of penicillin especially at the time of exposure to a streptococcus sore throat or when such is just beginning (Maliner and Amsterdam 1947 Goerner et al 1947 Milzer et al 1948 Massell et al 1948 Denny et al 1950) A daily oral dose of 100 000 to 300 000 units of penicillin has been found apparently effective (Pitt Evans 1950 Massell personal communication 1950) Similar preventive medicine may hopefully be practiced during acute infections or operative procedures (especially dental extractions) in the case of individuals with chronic rheumatic heart disease to ward off subacute bacterial endocarditis We still await however the final word as to the efficacy of these drugs in the prevention both of rheumatic fever and of subacute bacterial endocarditis

It is to be noted that neither penicillin nor streptomycin nor the sulfonamides have any favorable influence on the rheumatic process per se in fact the two latter may cause harm by their toxic effect

The *treatment of chorea* has been no more satisfactory than that of rheumatic fever Absolute rest and quiet, with good nursing care are more effective than any other measures Neither arsenic (e g Fowler s solution) nor the salicylates nor other drugs or serum appear to have any specific action in controlling chorea except for a promising recent experience with hormonal therapy (adrenocorticotropic hormone) For very severe (convulsive) chorea *magnesium sulfate intramuscularly, intravenously or intraspinally (in 25 per cent* solution) has been reported to have a sedative effect Phenobarbital (Luminal) barbital (Veronal) or other mild sedatives tincture of stramonium and continuous baths have also been recommended Febrile therapy by the use of foreign protein such as typhoid vaccine has also been used but this as a matter of fact may do harm by inciting an attack of rheumatic fever (Bland and Jones 1935)

The *convalescent care* of patients suffering from subacute rheumatic infections long continued and lasting for weeks months or even years has been a problem attracting much attention in recent years It is generally agreed that the active stage of the infection should be treated by rest in bed but there comes a time when it is difficult or impossible to be sure whether or not the infection has completely subsided In the case of restless children who feel well enough to run about and whose control is difficult at home much discretion must be used for such cases institutional care where the discipline is *good or supervision by able nurses may be essential during the active stage* of the infection When with the patient at rest in bed and not taking salicylates the temperature no longer rises over 99° F by mouth or 100° F by rectum the leukocyte count remains below 9 000 the sedimentation rate becomes normal the pulse rate keeps under 100 symptoms and signs of infection have disappeared and the nutrition is improved convalescence may be considered to have begun The further length of time after that during which rest in bed should be continued and the rapidity at which convalescence should be allowed to proceed to full normal activity should not be determined by any set rule (some have been suggested) but by the conditions in the individual case *After severe infection a minimum of several months of convalescence* should be prescribed before return to normal activity during this period a foster home or preferably the child s own home should be utilized with training of the family to cope properly with the situation

Removal of the patient to a *tropical climate* for example Puerto Rico (Coburn 1931) or southern Florida (our own experience Jones White Roche Perdue and Ryan 1931 to 1936 inclusive reported in 1937) from the north during the colder seasons has been found generally to act favorably in restoring health to children who show an active rheumatic state although beneficial as a rule *it cannot be regarded as specific and* it is an expensive

procedure often not justifiable Permanent residence in the tropics is preferable if a rheumatic family can readily arrange it

During convalescence massage and then the simple exercises of walking lifting and carrying will help to restore normal circulation and muscle function in the extremities Special graded exercises are not necessary if common sense is used Of great help in many cases has been recreational and even occupational therapy during convalescence and during the acute infectious stage membership in the In Bed Club for Children developed by Edith Terry of the Massachusetts General Hospital has greatly aided the morale of many hundreds of youngsters and their families

Tonsillectomy is advisable in many patients with chronic rheumatic heart disease provided their tonsils are infected or abnormally large and provided their hearts are in satisfactory condition to stand the operation as they usually are It is also to be recommended in many cases following active rheumatic infection *after* convalescence is well established It has been advised and carried out even during the acute stage of the infection apparently sometimes with immediate benefit but certainly sometimes with exacerbation of trouble this procedure is not to be recommended in most cases during the active process The prophylactic effect of *routine* tonsil removal in the case of rheumatic infection (rheumatic fever chorea heart disease) has however been disappointing there has been only slight evidence that it protects against either initial or recurrent attacks If the tonsils are however infected or enlarged or if there are repeated attacks of tonsillitis complete tonsillectomy should certainly be done in such cases it is undoubtedly beneficial in the long run The adenoid tissue in the nasopharynx should be removed with the tonsils If the operation is done in very young children it usually has to be repeated after some years because of the new growth of lymphoid tissue in the pharynx

Roentgen irradiation of the heart has also been tried in the therapy of active rheumatic infection (acute endocarditis and myocarditis) but its value has not been confirmed

Surgical treatment of chronic rheumatic heart disease is limited to but very few cases Despite the failure of mitral valvulotomy over 20 years ago renewed attempts are underway at present to apply surgical therapy to valve defects but it is as yet too early to gauge the results or even to prophesy the various technics that will be applied even plastic replacements have been suggested One special condition due to rheumatic heart disease has however already been dramatically helped by surgery and that is recurrent pulmonary edema secondary to tight mitral stenosis Three methods have been used which will be described in more detail in Chapter 26 They consist of (1) production of an atrial septal defect to relieve the high pressure in the left atrium and lungs (2) more practically and effectively to anastomose a right pulmonary vein to the vena azygos major and (3) probably best of all the surgical separation at their commissures of the adherent cusps of the mitral valve

For acute pericardial effusions paracentesis is necessary in rare cases only Chronic pericarditis of rheumatic origin is not the type requiring surgery in contrast to that due to tuberculosis

Prevention The prevention of rheumatic fever and thereby of rheumatic heart disease has become a practical reality It consists to date of several procedures (1) improvement of living conditions (2) protection against hemolytic streptococcus infection by contact with an infected individual (3) the prophylactic use of penicillin in the case of a susceptible person when there is such contact or when such infection begins in the individual concerned and (4) avoidance when possible of residence in climatic areas (high and cold in particular) where hemolytic streptococcus infection and rheumatic fever are common

Differential diagnosis Rheumatic heart disease in active form has to be differentiated from any acute infection especially if there happen to be heart murmurs The differentiation is generally easy in older children and adults because of joint and heart signs and symptoms but in very young children in whom the rheumatic infection is ill defined the problem may be a very difficult one to be solved only by continued and careful observation In young adults with chronic rheumatic heart disease it may sometimes be difficult to distinguish at first whether a new infection is a recurrent rheumatic attack or subacute bacterial (Streptococcus viridans) endocarditis The fewer joint symptoms longer course wider temperature swings greater anemia and eventual appearance of characteristic signs of embolism clubbed fingers splenomegaly and positive blood culture gradually allow the differentiation of subacute bacterial endocarditis from acute rheumatism The intradermal reaction to the toxic filtrate of the hemolytic streptococcus is generally positive in the rheumatic infection and generally negative in subacute bacterial endocarditis this is helpful but not conclusive It is important to note that the active rheumatic infection and subacute bacterial endocarditis may occur simultaneously in the same case (Kelson and White 1945)

Septic chronic or rheumatoid arthritis offers as a rule little difficulty in the differential diagnosis except when there happens to be a complication of heart disease or delayed A V conduction or when both diseases are present in the same case then careful study is needed Rare cases are however *insoluble there being no sharp boundary line especially between rheumatoid* arthritis and rheumatic fever

Chronic rheumatic heart disease must be differentiated from conditions like severe anemia which give rise to functional cardiac dilatation and murmurs This is generally easily done by the discovery of the underlying cause such as anemia and by the history which shows that the heart symptoms or signs appeared for the first time after the onset of the underlying disease

The rheumatic type of heart disease must be differentiated from other types not always an easy procedure The age the history of rheumatic infection family incidence the preponderant mitral valve involvement and the absence of other causative factors like syphilis thyrotoxicosis hypertension and cor

onary disease usually distinguish primary rheumatic heart disease from other types It is to be remembered however that two or three different factors may simultaneously cause heart disease in a given case much care and good judgment must be exercised not only to determine these causes but also to decide their relative responsibility

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CHAPTER 15

ACUTE AND SUBACUTE BACTERIAL (INFECTIVE) ENDOCARDITIS

Penicillin and other new specific therapeutic agents have already greatly reduced the seriousness of the diseases discussed in the present chapter and we may hope that eventually the reduction or even complete control of hemolytic streptococcus and other infections and of rheumatic and congenital heart disease may render it obsolete Much of what was printed in earlier editions of this book is now merely of historical interest

A discussion of acute and subacute bacterial (infective) endocarditis (malignant endocarditis) follows naturally after the last two chapters because bacterial endocarditis has been frequent in early adult life and has been in its subacute form an important complication of rheumatic and of congenital heart disease

These two types of cardiac infection have been called acute bacterial endocarditis and subacute bacterial endocarditis respectively because of their clinical characteristics This terminology is useful for general discussion and classification but not so satisfactory as is the terminology based on the specific causative bacteria the names of which should always be employed in preference to the general term provided we know what the bacteria are For example Staphylococcus aureus or pneumococcus endocarditis is preferable to acute bacterial endocarditis as a diagnosis and Streptococcus viridans or alpha hemolyticus endocarditis is a better term than subacute bacterial endocarditis The word infective is sometimes employed instead of bacterial and in former days both of these groups of infection of the heart were classed together as malignant endocarditis a designation with much justification because of the almost invariably fatal outcome in those days but unsuitable because of the customary restriction of the word malignant to new growths and because of the high recovery rate nowadays

In a large series of cases of acute and subacute bacterial endocarditis (199 cases with 138 autopsies) studied 25 years ago the responsible organisms were found as shown in Table 7 page 386

Acute and subacute bacterial endocarditis are alike in that they are both serious diseases attended by invasion of the endocardium by virulent organisms almost wholly of the coccus family, there may be a similar invasion of the walls of the great arteries (bacterial endarteritis) The duration and virulence of the diseases are the only points in which they differ clinically An arbitrary borderline of two months has been set between them If the infection is a violent one lasting but a few days or weeks it has been called acute bacterial endocarditis if it is slow in its course lasting over two or three months

Table 7

BACTERIA CAUSING INFECTIVE BACTERIAL ENDOCARDITIS

	Per Cent	
Streptococcus	57	
Pneumococcus	14	
Staphylococcus aureus	13	
Gonococcus	11	
Influenza bacillus	4	
Staphylococcus albus	1	(Thayer 1925)

it has been called subacute bacterial endocarditis Generally the latter is caused by one organism the Streptococcus viridans while the former is caused by any one of a large number of organisms Rarely a Streptococcus viridans infection is so rapid that it falls into the acute bacterial group and rarely one of the other organisms is so much resisted that it falls into the subacute bacterial group as happens infrequently in the case of the gonococcus or of the influenza bacillus

A high mortality was once characteristic of these diseases, prior to the use of penicillin early in 1944 but now recoveries are the rule and preventive measures are also highly effective especially in the case of the acute type Mild infection with these organisms resulting in demonstrable valvular deformity after recovery may possibly account for some of the chronic valvular disease found in cases without a history of a rheumatic infection but the extent to which this occurs is not actually known and must be regarded still as an open question In the present state of our knowledge it is reasonable to assume that the majority of cases of chronic nonsyphilitic valvular disease are rheumatic in origin

Finally there is a considerable number of cases of very fresh endocarditis of slight or moderate degree discovered only by the pathologist at postmortem examination of individuals dying of a great variety of diseases Such terminal endocarditis is of academic and pathologic interest alone for it usually cannot be diagnosed clinically and has little or nothing to do with the death of the patient We do not ordinarily designate under the term acute bacterial endocarditis this slight terminal endocarditis that has little or no clinical significance

ACUTE BACTERIAL ENDOCARDITIS

Acute bacterial endocarditis or endarteritis consists of an acute nonrheumatic invasion of endocardium or arterial endothelium either uncomplicated or as a part of other acute illness it is attended by the symptoms and signs of a severe infection and in days gone by ended often in fact usually in death in the course of two months but now recovery is the rule in the rare cases that still appear Cases in which it occurs number well under 1 per cent of all types of heart disease and of all types of endocarditis if we exclude the terminal endocarditis that has no clinical significance

Etiology *Cause* The bacterium responsible for this disease may be any one of several organisms generally either the Streptococcus hemolyticus the Staphylococcus aureus the Bacillus coli communis the pneumonococcus the gonococcus or the meningococcus These six infecting organisms had been found in acute bacterial endocarditis in Boston before the days of penicillin in the following relative frequency making up nearly 100 per cent of the total of cases the Streptococcus hemolyticus 43 6 per cent the Staphylococcus aureus 22 8 per cent the Bacillus coli communis 10 5 per cent the pneumococcus 8 4 per cent the gonococcus 4 2 per cent and the meningococcus 4 2 per cent (Phipps 1932 with additional data by Dexter personal communication a total of 48 autopsied cases of acute bacterial endocarditis)

Other bacteria that have been reported as rare causes of acute bacterial endocarditis are the Staphylococcus albus the typhoid bacillus the enterococcus the Micrococcus tetragenus the Bacterium acidi lactici the Streptococcus viridans the parainfluenza bacillus (Russell and Fildes 1928 Fox 1935) the plague bacillus Brucella melitensis (Malta or undulant fever bacterium) and the Micrococcus endocarditidis rugatus

These organisms enter the circulation and attack the heart usually in the course of severe illness elsewhere in the body such as pneumonia puerperal infection gonorrheal rheumatism abscesses pyemia tonsillitis and meningitis In one series of 400 fatal cases of pneumonia examined post mortem 22 instances of pneumococcus vegetative endocarditis were found (Menetrier 1919) and in another series of 337 fatal cases of pneumonia there were 14 cases of pneumococcus endocarditis (4 15 per cent) (Lord 1932) In a series of 402 fatal cases of puerperal fever acute streptococcus endocarditis was found 8 times (Ruiz and Garcia 1926) Happily all this is now essentially past history since there is at present specific therapy for almost all these primary infections

There is another source of infection that is not yet under adequate control and that is septicemia (especially with a staphylococcus) resulting from the self medication hypodermically by narcotic addicts (Hussey et al 1944 Luttgens 1949) In such cases there is usually no pre-existing valvular disease

Age Acute bacterial endocarditis may occur at any age from infancy to

old age but it is most frequent in the fifth decade It may rarely occur also in fetal life

Sex Males are more subject to the disease than are females (73 per cent males to 27 per cent females in Phipps series 1932)

Predisposing factors Although this acute cardiac infection may occur in hearts previously undamaged it is more likely to attack those hearts already diseased with rheumatic lesions or congenital defects or arteriosclerotic changes where the soil is more suitable (60 per cent of Phipps series 1932)

Pathology In acute bacterial endocarditis the valve cusps and frequently also the chordae tendineae and endocardium of atrium or ventricle (more commonly the left) and sometimes even the intima of aorta or patent ductus arteriosus are the site of the deposition of thrombi called vegetations these vegetations are of varying size sometimes as large as peas or beans and they consist of irregular masses of fibrin leukocytes and colonies of bacteria Any valve may be markedly involved but the pulmonary is only rarely affected In acute bacterial endocarditis though less strikingly than in rheumatic heart disease the valves of the left side of the heart are more frequently involved than those of the right side The aortic valve is about as frequently affected as is the mitral In a series of 23 cases of pneumococcus endocarditis the left side of the heart was involved alone in 18 the right side alone in 3 and both sides in 2 while the mitral valve was affected in 13 the aortic valve in 12, both mitral and aortic valves in 5 and the tricuspid in 5 in one of which the pulmonary valve also was involved (Lord 1932) in a series of 58 cases of gonococcus endocarditis the valve lesions were left sided in 48 and the aortic valve was involved in 35 of these (Lion and Levy Bruhl 1922)

Ulceration of the endocardium of valve or heart wall or of the wall of the aorta or other arteries is common in the more severe cases this is sometimes followed by perforation or aneurysms of cusps rupture of chordae tendineae abscesses of the valve rings and even by small aneurysmal cavities in the aortic or other arterial wall (called mycotic aneurysms)

With recovery scarring undoubtedly takes place but whether or not such recovery is responsible for a few of the cases of chronic aortic or mitral stenosis we have no certain knowledge

Coincident myocardial or pericardial disease is uncommon There may be found pyemic abscesses in the heart muscle or infarction due to coronary embolism arising from thrombi on the endocardium septic pericarditis is also possible in such cases but is rare

Symptoms The symptoms of acute bacterial endocarditis are simply those of any very severe infection with septicemia fever of septic type with wide swings as a rule often with normal temperature in the morning and 103, 104° (40° C) or 105 F in the evening chills and sweating prostration and delirium In addition, if the disease continues as long as a few weeks there tend to be symptoms from embolism caused by pieces of the endocardial thrombi blocking arteries to viscera extremities or brain and pain and other localizing symptoms such as hemoptysis from pulmonary infarction or hemiplegia from

cerebral embolism The involvement of the heart itself rarely causes symptoms

Signs The patient appears very sick with little to point to the source of trouble except for embolic phenomena and the appearance of anemia and heart murmurs (or their increase) if the disease lasts long enough Sometimes there are no definite signs the fever being accounted for by other evidence of infection while the heart condition is discovered only at postmortem examination There is usually a high (polymorphonuclear) leukocytosis of 20 000 to 30 000 or more unless the infection has completely overwhelmed the resistance of the patient A secondary anemia develops rapidly but does not become so severe as in the subacute variety of bacterial endocarditis because of the short duration of the disease There may be petechial hemorrhages into the skin and in rare cases even extensive purpura There may be defective atrioventricular conduction shown by increase of the *P R* interval of the electrocardiogram beyond 0 2 second but this is rare Arrhythmias are very uncommon The most important method of study is that of blood culture In the presence of this disease a positive blood culture is usually obtained at the second or third attempt if not at the first the cause of the infection is thus discovered

Course and prognosis Acute bacterial endocarditis formerly progressed in rapid strides to a fatal termination in the course of days or weeks Death was usually the result of toxemia but sometimes it came from embolism of brain lung or coronary circulation Very infrequently was it due to heart failure The beginning of effective specific therapy by penicillin the sulfonamides and other medication during the past decade has changed the picture completely so that now fatalities are uncommon and acute bacterial endocarditis is usually cured before it starts by the control of the underlying disease whether pneumonia meningitis gonorrhea or other acute infection Thus the diagnosis of acute bacterial endocarditis has now become not only very difficult but also very rare It can still be suspected by the careful physician who notes the onset of the heart murmurs of valvular involvement during the course of pneumonia or sepsis and who observes the persistence of these murmurs and the development of cardiac enlargement on recovery

Complications Embolism secondary anemia and heart failure have already been noted as important complications Another occasional complication that may be serious or even fatal is the tendency to hemorrhages such as may occur in any fulminating infection—purpura of skin sclerae and mucous membranes and bleeding from nose mouth lungs or gastrointestinal tract

Treatment In the second edition of this book fourteen years ago it was stated that there is no specific treatment for the disease except in the very rare case of meningococcus endocarditis when the administration intravenously of active antimeningococcus serum may effect a cure that when the pneumococcus of type 1 or type 2 is responsible it would seem rational to inject antipneumococcus serum that in most cases of acute bacterial endocarditis all kinds of drugs vaccines and serums have been tried in vain that

transfusions also have failed and that the rare recovery except when antimeningococcus serum may help is due apparently to the patient's own resistance which is to be supported by every measure at one's command chiefly by good nursing care, food, quiet and avoidance of the administration of drugs except to relieve discomfort ' A great advance was noted in the third edition seven years ago consisting of the use of the sulfonamide drugs (sulfanilimide sulfapyridine, sulfathiazole, and sulfadiazine) which by controlling the underlying infections from pneumococcus, gonococcus streptococcus and staphylococcus prevented, in some cases at least this serious in fact previously fatal complication of acute bacterial endocarditis and now today we can happily record another, perhaps final spectacular advance since penicillin has appeared to help to wipe out this dread disease

Differential diagnosis The two chief difficulties in diagnosis come (1) from easy confusion with the subacute variety of bacterial endocarditis and (2) from confusion with severe infection of other nature especially with persistence or recurrence of the original disease from which the endocarditis comes In the former case the virulence of the acute variety of bacterial endocarditis its shorter course the recent history of other illness and blood culture findings generally make differentiation clear In the latter case the differentiation may be impossible only the development of embolic phenomena of severe anemia or of murmurs pathognomonic of valvular involvement (usually an aortic diastolic murmur) may point eventually to acute bacterial endocarditis It is impossible to distinguish the rare case of recovery with chronic valvular disease from one of rheumatic origin unless the pulmonary valve has been affected or the case has been observed during its development in the course of some serious infection like pneumonia

SUBACUTE BACTERIAL ENDOCARDITIS (ALSO CALLED SUBACUTE INFECTIVE ENDOCARDITIS CHRONIC ULCERATIVE ENDOCARDITIS AND ENDOCARDITIS LENTA)

Subacute bacterial endocarditis as a clinical entity is much more common than is the acute variety of malignant endocarditis It consists of the invasion of the heart—chiefly of the valves—by the Streptococcus viridans rarely by the gonococcus or influenza bacillus until recently it resulted fatally after a lingering illness Its frequency and seriousness make it of great importance In New England 20 years ago it occurred in 1 to 2 per cent of all cardiac patients (White and Jones 1928) in 7 to 8 per cent of persons with congenital cardiovascular defects (Abbott) and in about 5 per cent of cases of rheumatic heart disease Because of its seriousness subacute bacterial endocarditis has a relatively high hospital incidence in comparison with rheumatic fever for example in the years 1928 to 1931 there were 177 cases of subacute bacterial endocarditis admitted to the larger Boston hospitals in contrast to 772 cases of rheumatic fever (Morrison 1932) The advent of the sulfonamide derivatives ten years ago altered the situation for the outlook

was no longer entirely hopeless as it had been a moderate number of cures were recorded but the disease was still nearly 95 per cent fatal It was early in 1944 that with proof of the efficacy of penicillin (Loewe) the outlook suddenly brightened and now recovery is possible in at least 80 per cent of the cases Despite this great change in fact because of it a clear recognition of the details of the disease has become all the more important since the earlier the diagnosis is made the sooner the curative treatment can be started and the less will be the added damage to the heart and the risk from the common and serious complications such as embolism

Etiology *Cause* The organism responsible for subacute bacterial endocarditis is in 90 to 95 per cent of the cases the Streptococcus viridans (Schottmuller 1910) and in the other 5 to 10 per cent the gonococcus influenza or parainfluenza bacillus enterococcus or Brucella abortus The typhoid bacillus has also been reported to give rise to a long-drawn-out endocarditis There may be a mixed infection as by gonococcus and streptococcus (Orgain and Poston 1942 Olinger 1948) or there may be more than one strain of viridans streptococci in the same case (MacLean and Howell 1947) All these other organisms especially the gonococcus can cause a short virulent acute bacterial endocarditis but the Streptococcus viridans rarely does so

Predisposing factors The chief predisposing factor is chronic heart disease particularly old rheumatic valvular disease (in about 80 per cent of the cases) and congenital cardiovascular defects (in about 10 per cent of the cases) especially in those with either bicuspid aortic valves (9 of 32 cases of Abbott s series and 11 of 52 of Gelfman and Levine s series) or ventricular septal defects (13 of 50 cases and 13 of 31 cases respectively) or patency of the ductus arteriosus (21 of 92 cases and 4 of 14 cases) or coarctation of the aorta (7 of 70 cases and one of 10 cases) in contrast to atrial septal defects (2 of 68 cases and none of 45 cases respectively Abbott and Gelfman and Levine 1942) but a previously undamaged heart may infrequently also be the site of this disease Rarely aortic valves damaged by syphilis may be involved in subacute bacterial endocarditis but in such cases there may be a coincident rheumatic valve lesion

Focal infection as in diseased teeth tonsils and gums can be a predisposing factor (Weiss 1934) dental extractions are more commonly followed by subacute bacterial endocarditis than are any other recognizable events There is a clear reason for this as indicated by the findings of Okell and Elliott (1935) in 40 instances after multiple tooth extractions in the presence of extensive disease of the gums positive blood cultures were obtained in 30 (75 per cent) in 60 instances after multiple tooth extractions in the presence of a moderate degree of gum disease there were positive blood cultures in 42 (70 per cent) and in 38 instances of the extraction of one or more teeth without detectable gum disease there were 12 positive blood cultures (34 per cent) The more often one inquires specifically about dental work or infection prior to the onset of subacute bacterial endocarditis the more often one finds it (up to about one third of the cases)

The mechanism of the endocardial involvement in subacute bacterial endocarditis has been variously considered Direct blood stream infection of the *endocardium damaged of old with small thrombi or ulcerations* as footholds for the streptococci that happen to be circulating in the blood is probably the usual mode of involvement rather than the introduction of these organisms to the endocardium through blood vessels in the valves but it is possible that both methods of infection exist *Although the Streptococcus viridans is an* occasional invader of the blood stream even in normal persons it causes no disease unless it enters in large numbers (as through foci of infection) or unless conditions favor its lodgment and growth as in individuals with chronic heart disease

Age The age at which subacute bacterial endocarditis occurs varies from early childhood to old age it is commonest between the ages of fifteen and thirty years Of 250 cases in Kelson and White's series (1945) 6 were under ten years 42 between ten and twenty 79 between twenty and thirty 53 between thirty and forty 39 between forty and fifty 21 between fifty and sixty and 10 over sixty The youngest cases on record are one and one half years old (Goetsch 1938) two and one half (complicating congenital heart disease) and five years old but the disease is very rare in young children The oldest cases were eighty two years of age a man who had apparently sclerotic valvular changes as a background of his infection (Willius 1940) and eighty seven years (Zeman 1945) Streptococcus viridans bacteriemia without endocarditis has been reported in two infants shortly after birth the mothers being ill with subacute bacterial endocarditis themselves (Walser 1928) A collection from the literature has been made (Rost and Fischer 1928) of 64 cases under the age of fourteen years

Sex Subacute bacterial endocarditis occurs somewhat more often in males than in females in Kelson and White's series (1945) it was found in 161 males and 89 females and in a series of 328 cases collected by Blumer from the literature the ratio was 60 per cent males to 40 per cent females (Blumer 1923)

Other factors Other factors such as race climate and social and economic *status are relatively unimportant compared to that of the presence of chronic* heart disease mentioned above except as they favor the predisposing cause namely rheumatic involvement However it is possible though not yet proved that any illness accident or exposure to cold and wet or to strain may help to precipitate the disease by favoring the bacterial invasion

Pathology The pathologic picture in subacute bacterial endocarditis is primarily that of involvement of the endocardium of valves by the deposition of irregular masses of fibrin leukocytes erythrocytes and platelets enclosing bacteria and products of bacterial degeneration, called vegetations (Figures 87 and 88 see opposite page) These vegetations are larger than the thrombi in rheumatic endocarditis but they may not be so large as those of acute bacterial endocarditis The chordae tendineae and left atrium and left ventricular endocardium are frequently involved by a spreading of the infection from the valve

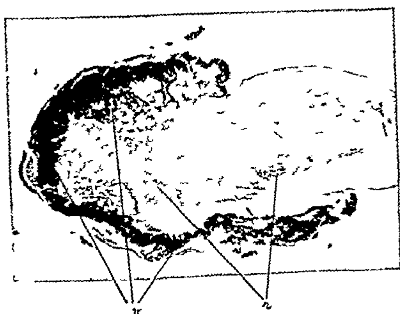


FIG 87 Microphotograph showing low power magnification of the cross section of the end of a cusp of the mitral valve infected by the Streptococcus viridans in subacute bacterial endocarditis Note vegetation (v) encircling the cusp end and consisting mostly of masses of bacteria and fibrin (stained black) Also note inflammatory leukocytic reaction (r) in the cusp itself



FIG 88 Photograph showing subacute bacterial (infective) endocarditis with vegetations on mitral valve and endocardium of left atrium (Kindness of Dr Ronald Grant, Guy's Hospital London)

cusps or by contact with the cusps that is, where the heart wall touches these vegetations on the cusp during the heart cycle The intima of the aorta may also be infected either where aortic valve vegetations are in contact with it or elsewhere An arteriovenous aneurysm may become infected by the Streptococcus viridans Finally congenital defects such as patent ductus arteriosus coarctation of aorta and especially interventricular septal defects and bicuspid aortic valves may be the site of invasion by the Streptococcus viridans

There may result from this inflammation of the endocardium an extension of the process into underlying tissues with deep ulceration or perforation or aneurysm formation in the valve cusps or local ulceration and aneurysm of the aorta (even with rupture) This type of aortic aneurysm like that resultin from acute bacterial endocarditis, is called a *mycotic aneurysm* In very rare cases the process may cause an aneurysm in or a perforation through the ventricular septum or from left ventricle into right atrium or even a rupture of atrial wall Also rarely invasion of the upper ventricular septal region may damage the atrioventricular bundle (of His) to cause heart block The vegetations sometimes grow very large or elongated and if this occurs on the aortic valve the vegetations may partially block the mouths of the coronary arteries

The valves of the left side of the heart are much more frequently involved than are those of the right side and the mitral valve oftener than the aorti though the great preponderance of mitral over aortic valve involvement seen in rheumatic heart disease does not hold here Pulmonary valve involvement is rare in subacute bacterial endocarditis in contrast to its involvement in acute bacterial endocarditis In a series of 90 autopsied cases of subacute bacterial endocarditis in which there was a specification of the valves that were involved in the process the mitral valve alone was affected in 25 the aortic valve alone in 18 both mitral and aortic in 38 mitral aortic and tricuspid in 2 all four valves in 1 pulmonary and aortic in 2 tricuspid and ventricular septal defect in 1 pulmonary and ductus arteriosus in 1 pulmonary aortic and ductus arteriosus in 1, and only the mural endocardium in the remaining 1 (Morrison 1932)

As already noted in the majority of cases Streptococcus viridans endocarditis is superimposed on chronic rheumatic valvular disease It is probable that in communities where rheumatic heart disease is infrequent the predisposing factor of congenital defects is as important as is that of rheumatic valvular disease and in such communities one would expect to find the total incidence of subacute bacterial endocarditis considerably reduced in comparison with that in rheumatic areas Out of 203 cases of subacute bacterial endocarditis analyzed in Boston 134 had clearly and others probably a rheumatic background 11 had congenital defects 3 an underlying syphilitic process and one a definite atherosclerotic basis (Morrison 1932) Markedly stenosed valves are less frequently attacked by subacute bacterial endocarditis the less slightly deformed valves in chronic rheumatic heart disease are the ones found at autopsy to be more often the site of this fatal complication and they are the ones which during life give rise to the murmurs of valvular regur

gitation (the systolic murmur of mitral origin at the apex and the diastolic murmur of aortic origin at the base)

Pericarditis in subacute bacterial endocarditis is rare but myocardial lesions have been reported (Bracht and Wachter 1909 Saphir 1946) consisting of diffuse inflammatory changes and of areas of infiltration in the interstitial tissue of the myocardium These areas however are also found in other cardiac infections and include the Aschoff body which may or may not indicate the presence of a coincident rheumatic heart infection in some cases Saphir has also described foreign body granulomas caused by calcific emboli arising from healed vegetations on the aortic valve in patients recently treated with penicillin or the sulfonamides

After recovery from subacute bacterial endocarditis the extent of chronic valvular disease may be increased Since however most of the valvular deformity is usually the result of previous rheumatic infection careful observation of the state of the heart before or at the onset of the subacute bacterial endocarditis is essential before it can be said that this disease caused or increased the valve deformity in a given case

Symptoms The symptoms of subacute bacterial endocarditis are like those of any infection but are less severe than in acute bacterial endocarditis Fever of varying grades occurs sometimes almost none at all and sometimes with wide daily swings of septic type as for example normal or subnormal temperature in the mornings and high fever (to 104° F or 40 C) in the evening Fever may however be absent for days at a time and then recur at intervals Chills and sweats are common Anorexia malaise prostration and loss of weight and strength are usual although for days or even weeks at the onset there may be merely a feeling of fatigue with little fever When embolism begins coming from thrombi in the heart local pain and other symptoms appear depending on the organ or the part of the body affected Splenic renal and cerebral infarctions are common With increasing anemia there may be hemorrhages into skin and from nose lungs and stomach—in addition to the embolic phenomena Finally if the disease is not brought under control the toxic state increases and weakness and mental confusion may become marked before death ensues or myocardial failure may develop with dyspnea or hepatic congestive pain or both if the infection is exhausting whether or not it is itself cured However with successful penicillin therapy at a relatively early stage of the disease nowadays, alert medical attention can in the majority of cases stop the process before any important complications take place

Signs The characteristic signs of the disease are fever a pallor due largely to secondary anemia and sometimes referred to as cafe au lait (Libman) petechial hemorrhages into the skin mucous membranes and conjunctivae splenomegaly clubbing of the fingers and evidence of valvular or congenital heart disease Rarely are all these signs pronounced in any given case usually the diagnosis must rest on two or three only generally supported however by a finding of the Streptococcus viridans by blood culture

The superficial *petechial hemorrhages* may be found anywhere on the body

and should be searched for carefully, they may be limited to the conjunctivae to the chest or elsewhere They are most commonly found on the forearms and hands, when located under the nails they are linear in shape and have been designated 'splinter hemorrhages They come and go often in crops in a given area, each spot rarely lasts more than a few days beginning as a small reddish or purplish dot under the skin not disappearing on pressure but gradually fading away within a week The spots vary in size usually from that of a pin point to that of the head of a large pin They may be produced in the forearm from the compression of the upper arm by a blood pressure cuff Thus they are evidently the result of damage to vessel walls by a toxin which allows leakage of blood whenever pressure trauma or some other factor favors it The petechiae are therefore related rather to a hemorrhagic tendency of which a common sign is nosebleed than to embolism Petechial hemorrhages although very common in subacute bacterial endocarditis are not pathognomonic of the disease they are also found not uncommonly in acute rheumatism

There is another sign of vascular origin often of value but not found in all cases of subacute bacterial endocarditis tender fingers and toes This is due most commonly to embolism of or hemorrhage from a small vessel in a finger tip or in a toe and consists of a deep painful purplish slightly swollen indurated area the size of a pea or smaller in the pulp of the end of the finger This lesion comes suddenly and disappears gradually in the course of a few days It may be isolated or there may be several such lesions at the same time or in succession Either fingers or toes may present this sign but more commonly the fingers are affected

The so-called Osler s node (Osler 1909) as described first by Mullen of Hamilton and later by Osler himself is a much rarer phenomenon it consists of a raised red nodule (never hemorrhagic) in the skin of finger or toe and not beneath it ½ to 1½ cm in diameter with a whitish point in the center and lasting a day or two

Still another sign and much the most important of those found in the fingers or toes of patients with subacute bacterial endocarditis is *clubbing* This condition also found in congenital heart disease and certain pulmonary diseases is shown in Figure 63 page 298 In subacute bacterial endocarditis it is very variable in occurrence and degree Clubbing is present in some measure in three quarters of all the cases but is well marked in only one half or somewhat less being most evident in the cases with enlarged spleens It does not appear at the onset of the disease but only when it is well advanced after the first few weeks Why it should occur in this disease has not been discovered but it is likely that local disturbance of the circulation (instead of general anoxemia with cyanosis as in congenital heart disease) causes capillary dilatation and increased soft tissue growth Instead of cyanosis there is usually increased redness of the bulbous finger tips When present clubbing is an important sign and should always be heeded but care must be taken not to confuse it with congenital or occupational abnormality of shape of the fingers Although the

toes may be clubbed as well as the fingers their clubbing is generally less obvious Clubbing recedes with recovery and disappears completely

Splenomegaly is common in subacute bacterial endocarditis and its presence is a very helpful sign However in about a third of the cases the spleen cannot be felt on physical examination Its enlargement when evident is usually not great, a firm nontender edge being felt just below the left costal border On rare occasions it may become large enough to extend almost to the umbilicus Like clubbing of the fingers splenomegaly usually clears up with recovery

The presence of evidence of *chronic valvular disease* or of *congenital defects* is usual and is somewhat corroborative One finds commonly an apical systolic murmur of mitral regurgitation occasionally the early diastolic murmur of aortic regurgitation and less commonly the murmurs of mitral stenosis aortic stenosis or congenital defects Sometimes an important murmur develops in the heart under observation indicating the onset or the increase of valvular deformity during this infection There is usually slight cardiac enlargement The heart may however appear normal on physical examination during most and rarely during all of the illness one may be misled thereby In such cases there may be endocarditis of a congenitally bicuspid aortic valve without enough actual valvular deformity to produce significant murmurs

Arrhythmia due to atrial fibrillation complicating subacute bacterial endocarditis was formerly thought to be extremely rare in recent years it has been found that their coexistence occasionally though still uncommonly takes place for example McDonald (1946) has reported 36 cases of atrial fibrillation (12 6 per cent) among 286 patients with subacute bacterial endocarditis Of these 36 cases 24 were carefully analyzed 3 showed paroxysmal arrhythmia and 21 permanent Of the 21 5 had the infection first, 6 had the arrhythmia first and 10 had both when first seen Premature beats are occasionally found but are of little importance The rare occurrence of delayed atrioventricular conduction (heart block) suggests extensive involvement of the interventricular septum Pericarditis is extremely rare in subacute bacterial endocarditis

Blood pressure roentgenologic and electrocardiographic studies show little or nothing abnormal except for evidence of underlying valvular disease congenital defect or heart block which may or may not be due to the subacute bacterial endocarditis

Blood studies are of much importance *Secondary anemia* is common if the disease lasts six weeks or more with red cell count between 3 and 3½ millions and hemoglobin at about 60 per cent somewhat lower figures of 2 to 3 millions of red cells and 40 to 50 per cent hemoglobin are also found but less frequently In rare cases the red count may drop to one million or less with hemoglobin of about 30 per cent A polymorphonuclear leukocytosis of slight to moderate degree (12 000 to 16 000) is common when there are complications such as embolism to spleen or elsewhere infrequently it is higher but more commonly it is lower often being recorded at a normal figure The blood smear shows achromia of red cells but only rarely polychromatophilia or change in size or shape of the cells The platelets are normal In a certain

small percentage of cases, perhaps 10 or 15 per cent, there are found in the blood smear occasional large endothelial phagocytic cells which are also found sometimes in other diseases their presence is somewhat helpful in corroborating the diagnosis The sedimentation rate is usually accelerated

Blood cultures carefully taken and repeated once or twice if necessary should be positive for the Streptococcus viridans in about 90 per cent of the cases A suitable culture medium is hormone broth with hydrogen ion concentration of *p*H 7 6 It is of interest to prepare pour plates in order to get some idea of the quantity of organisms by the number of colonies per plate which may vary from one to many Blood is collected in citrate flasks (½ cc of 4 per cent sodium citrate in a 50 cc Pyrex flask) from which 2 cc and two 1 cc samples are pipetted into tubes of melted nutrient agar which is cooled to 45 C after the tubes are rolled a few times the mixtures are poured into Petri dishes and the colonies are read after two and four days (kindness of Dr Louis Dienes) Cultures of venous blood usually suffice but on rare occasions cultures of bone marrow are positive when blood cultures are negative Arterial blood cultures are least satisfactory (Salazar Mallen, et al, 1947)

Titration of immune bodies in the blood in patients with subacute bacterial endocarditis has shown a high degree of such bodies much greater as a rule *than in the blood of the normal control This test may perhaps prove helpful* in establishing the diagnosis

The Wassermann reaction has sometimes been found positive in subacute bacterial endocarditis in the absence of syphilis this possibility should be remembered

The urine is not remarkable except for the frequent and important finding of numerous red blood corpuscles in the sediment There usually is not enough blood to appear macroscopically This finding in the sediment has been ascribed to renal infarction by multiple small emboli At postmortem examination glomerular lesions are frequently found (Baehr 1912) However it is probable that much of the blood in the urine is the result of minute hemorrhages comparable to those in the skin (petechiae) Albuminuria is commonly present if there is much fever or bleeding

Course and prognosis The gradual insidious onset of this disease often prevents any exact determination of the time of its beginning There may be a feeling of increasing fatigue and loss of appetite and sometimes there are vague joint and muscle pains the victim may appear pale listless and run down" for a few weeks before fever or other symptoms force him to bed or to ask for medical advice Months sometimes elapse with no definite idea of what is wrong Usually however in the early weeks of the illness the temperature reaction anemia enlarged spleen or clubbing of the fingers and heart signs and blood culture show the presence of this serious illness Prior to 1944 the symptoms and signs would steadily increase with development of embolic phenomena and death often the result of complications commonly ensued a few months to a year or more after the onset of the disease the average duration of the illness being about six months

Recovery prior to 1939 occurred in less than 1 per cent of all cases of sub acute bacterial endocarditis rose to 5 or 6 per cent when the sulfonamides were introduced in maximal and very disagreeable dosage and five years later in 1944 abruptly increased to a little over 50 per cent with the advent of moderate but still inadequate amounts of penicillin Slowly in the five years that have elapsed since then when penicillin became available in larger and larger amounts and with increasing realization of the need of massive doses early in the disease and with the help of allies such as streptomycin at least 80 per cent of the patients have become curable It is likely that the ultimate figure will approach 90 but it is also probable that there will always be fatalities due to four causes (1) heart failure resulting from the extent of the heart disease itself plus the added strain of the infection and its treatment (2) embolism to brain or elsewhere and (3) intercurrent acute rheumatism these three causes operating even in cured patients and finally (4) resistance in a few cases to all specific therapy

It is to be remembered that a finding of the Streptococcus viridans in the blood by culture does not alone establish the diagnosis of subacute bacterial endocarditis even if chronic valvular disease (or a congenital cardiovascular defect) or fever is also present the presence of all three of these findings is however almost conclusive in a given case Positive blood cultures have been found without fresh endocarditis indicating that there is an illness of other nature present and not malignant endocarditis A preponderant group of signs should be present to establish the diagnosis of subacute bacterial endo carditis The clinical course is the most important clue For full reliance on blood cultures several (at least 3 or 4) should be found positive

There has been a very interesting small group of cases of subacute bacterial endocarditis mostly of historic interest now that became bacteria free but nevertheless went on for the most part to a fatal termination from uremia or heart failure they were characterized by the subsidence of fever negative blood cultures anemia brownish color of face and particularly severe glomerulone phritis (Libman 1913)

Finally advanced subacute bacterial endocarditis may be wholly or in large part symptomless prior to the occurrence of serious embolism which in the case of a woman 31 years old led rapidly to death from coronary occlusion (West 1931)

Complications The chief complications of this disease are due to infarction of various organs from emboli that arise from the intracardiac (chiefly valvu lar) thrombosis If these emboli are large and affect vital tissue a speedy death may follow The most important infarctions are those of the heart itself by coronary embolism of brain and of kidneys Cardiac infarction is very rare hemiplegia or paralysis of lesser extent is not uncommon after cerebral em bolism and hematuria may result from renal infarction or simply from leaking blood vessels Hemorrhage of any serious moment is not often seen in this disease rarely it may complicate cerebral embolism and result fatally The renal damage may infrequently lead to uremia and death in a case of subacute

bacterial endocarditis A large embolus may obstruct an important artery to an extremity like the femoral popliteal tibial brachial or digital artery but rarely causes gangrene with need of amputation The spleen is one of the most common sites of infarction this explains the very frequent severe pain in the region of the spleen in patients with subacute bacterial endocarditis Mesenteric infarction may occur and it has been suggested that some pulmonary signs may be due to embolism of bronchial arteries Pulmonary infarction is not common inasmuch as the endocardial vegetations are generally or preponderantly on the left side of the heart but with thrombi in the right heart chambers this too can occur A long course of febrile illness in a patient with congenital heart disease affecting the right heart chambers complicated by pulmonary infarcts strongly suggests subacute bacterial endocarditis in such cases blood cultures may fail to show the Streptococcus viridans until late in the disease and clubbing of the fingers and splenomegaly may be wanting (Blumgart 1933)

Heart failure of congestive type is sometimes but not often the cause of death it is frequently present in slight or moderate degree brought on by the strain of infection and anemia in a heart already damaged rarely is there enough additional damage to the heart from this infection to cause failure directly Angina pectoris may rarely occur due to blocking of the mouths of the coronary arteries by the vegetations on the aortic valve, or to the added effects of aortic regurgitation and anemia Atrial fibrillation occurs infrequently and heart block appears in rare cases

Active rheumatism in the form of rheumatic fever or even of pancarditis may complicate subacute bacterial endocarditis apparently excited by it in some cases and pre-existing in others it was thought to be a complication in at least 17 and perhaps 4 more of Kelson and White s series of 250 cases (1945)

The secondary anemia itself if not well controlled by transfusion may become a grave complication favoring a fatal outcome In his weakened condition the patient may fall a victim to a complicating infection like pneumonia

Finally it is of some interest to note that pregnancy childbirth and the puerperium may progress without any material difficulty despite subacute *bacterial endocarditis (Mengert 1933) although there may be Streptococcus* viridans bacteriemia in the infant (Walser 1928)

Treatment In the first three editions of this book many different medicines and other empiric therapeutic measures were discussed but the only treatment that gave any promise at all was that with the sulfonamides especially sulfadiazine which was the least toxic while effecting rare cures When the sulfonamides were forced beyond the point of endurable toxic results there was a *slightly higher percentage of recoveries Doses of 2 gm of a* sulfonamide followed in two hours by another 2 gm initially and then 1 gm every four hours until the blood level reached close to 10 mg per 100 cc followed by adjustment of the dose to maintain that level in the course of a fortnight or two resulted

in a few cures Such supplementary therapy may still be of value when penicillin and streptomycin are alone or in combination ineffective Heparin and Dicumarol were added to this sulfonamide therapy in the early days with the thought that they might prevent the deposition of new thrombi on the endocardium while those already present were being sterilized but practical experience during recent years has indicated that such addition to the treatment has not resulted in any gain and instead has been troublesome expensive and even on occasion harmful

It is of historic interest merely to insert herewith without further comment except to note their failure the imposing list of drugs and other therapy tried years ago in the vain effort to cure this dread disease arsenic in various forms mercury gentian violet salicylates antiseptics of all kinds vaccines serums transfusions including those from immunized donors production of sterile abscesses splenectomy electrotherapy diathermy and hyperthermia A few of these measures have had on occasion a somewhat helpful though not curative effect transfusions have so acted when there has been a severe anemia and both splenectomy and hyperthermia have had their advocates

Happily today one can be brief and explicit about therapy that is effective in the great majority of cases as the result of the discovery reported by Fleming in 1929 that Penicillium notatum a common mold contained a potent antibacterial substance of its purification and application by Florey and his colleagues in 1940 and of its curative effect in subacute bacterial endocarditis by Loewe in 1944 After the diagnosis has been established as early in the disease as possible or if not proved at least considered probable after careful study penicillin should be administered at once in adequate dosage and continued as a rule for six weeks with a range of four to eight, or as much longer as may be deemed necessary in any particular case A dose of 500 000 to 1 000 000 units a day should be given parenterally if for any reason oral medication is given the daily dose must be 5 to 10 times greater to produce the same beneficial effect If after a week or ten days there is no obvious effect of the 500 000 to 1 000 000 unit dose on fever clinical course or blood culture the daily amount should be multiplied five times Even as much as 20 000 000 units a day for weeks has been necessary to effect a cure in rare cases

Common mistakes quite natural in the early days of such therapy because of the limited supply of the penicillin were to give too little at the start and to increase the size of the dose too slowly and too cautiously It is far wiser to give a larger amount than may be necessary at the beginning rather than to allow the infection to continue too long with the hazard of serious complications It is however best of all routinely to adopt the procedure of in vitro testing of the sensitivity to penicillin of the causative organism whether Streptococcus viridans or not since there has been shown to be a very definite relationship between this sensitivity and the curative dosage (Hunter 1946 Clark et al 1948) The great majority of the strains of the Streptococcus viridans are inhibited by 0 1 unit of penicillin per cubic centimeter of culture

medium and so do not need maximal dosage but a few require 0 2 to 0 5 units and a very few up to 1 unit or more It has been helpfully advised that for the first that is the more sensitive group a daily dose of 500 000 units be given for the second that is the intermediate group a dose of 1 to 2 million units, and for the third the most resistant group a dose of 5 to 20 million units a day If these maximal doses are still ineffective adjuvant treatment with caronamide or streptomycin is in order (see below)

Various methods of administration of the penicillin have been introduced and they all have had their advocates as may be found on consulting the Bibliography of this chapter Intramuscular injections in sterile saline or aqueous solution every two to four hours (usually three) day and night were in use most frequently and proved to be quite practical and effective Constant intramuscular and intravenous drips were also curative earlier and had the advantage of producing a more constant blood level but the disadvantage of inconvenience Penicillin in oil and beeswax proved helpful in establishing a fairly uniform absorption and blood concentration although without high levels (Hewitt 1947 Hoffman et al 1947) this procedure was especially convenient because it reduced the number of injections needed intramuscularly to two in twenty four hours and was recommended in particular for prophylaxis as in the case of dental extractions Recently there has come into more or less routine use a preparation of penicillin with procaine (which has a beneficial twofold effect of rendering the injection painless and slow in absorption) which can be very conveniently and effectively injected intramuscularly in the dosage of 300 000 or 600 000 units every six hours giving satisfactory total daily doses of 1 200 000 or 2 400 000 units respectively

Another important means of maintaining a more or less uniform and especially a higher (threefold or more) concentration of penicillin in the blood particularly useful in obstinate cases not responding well to lower concentrations is by adding caronamide or benemid which blocks the ordinarily rapid excretion of penicillin through the renal tubules (Beyer 1947 Boger et al 1947 1949 and 1950 Loewe et al 1947 Meads et al 1948 Burnell and Kirby 1951) Four grams of caronamide are given orally every three to four hours or ½ gm of benemid every six hours for days to weeks in order to produce a blood serum concentration of approximately 30 mg per 100 cc which is necessary in order to maintain a threefold or more increase of penicillin level The drug must be used with some caution however in patients who have any suspicion of reduced kidney function beforehand and probably not at all when serious kidney disease is present Also toxic symptoms such as nausea and vomiting may be induced in some cases However the use of caronamide and benemid has resulted in cures by penicillin in cases not responding well without it

Finally in cases fortunately very few in number in which penicillin is ineffective it may be necessary to resort to streptomycin alone or in addition or even to add sulfadiazine This applies to organisms particularly gram negative bacilli and certain gram positive cocci which are very insensitive to

penicillin In such cases after the in vitro and brief in vivo testing with penicillin and in vitro testing with streptomycin the latter should be injected intramuscularly in the dosage of 0 5 to 1 0 gm (preferably the larger dose) every six hours for days to weeks depending on the clinical progress and toxic symptoms This gives a blood concentration of streptomycin of some 10 to 20 units (or micrograms) per 100 cc which is as a rule far greater than the in vitro sensitivity of the organism causing the disease There are two difficulties which render streptomycin much less satisfactory to deal with than penicillin (1) the toxic effects which include especially vertigo which may be permanent secondary to labyrinthitis fever dermatitis and pruritis and (2) increasing resistance of the organism to the drug Despite these disadvantages there are well-established cures of subacute bacterial endocarditis by streptomycin Much more rarely and more or less as a last resort sulfadiazine may be added to penicillin or streptomycin or both in the oral dosage of 4 gm initially or 2 gm repeated in two hours followed by 1 gm every four hours until the blood level reaches 10 mg per 100 cc with continuation at that level and finally other antibiotics besides penicillin are worthy of trial in the case of unusual and rare infectious agents not amenable to penicillin

Mention should be made of course of the importance of the best nursing care in the treatment of this disease of patient but optimistic attitude of both doctor and victim during the tedious weeks of therapy and of the early recognition and treatment of complications such as congestive heart failure by the use of digitalis low sodium intake and diuretics In very rare cases cure of infected peripheral blood vessels as in instances of mycotic and arteriovenous aneurysms has been effected by surgical excision

Differential diagnosis The four conditions from which it may be difficult to differentiate subacute bacterial endocarditis are (1) active rheumatic heart disease (2) acute bacterial endocarditis (3) infections of other nature with or without chronic valvular disease and (4) blood diseases or severe anemia secondary to some other infection like malaria The duration and average severity of subacute bacterial endocarditis the relative infrequency and unimportance of joint pains or swelling the clubbing of the fingers when present the slight but usually not great enlargement of the spleen the moderate grade of secondary anemia the finding of the Streptococcus viridans in the blood stream and particularly the frequency of embolism in an infection not very virulent in nature distinguish this disease with little difficulty from others It is however important to remember that the various conditions cited above may coexist in the same case

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CHAPTER 16

CARDIOVASCULAR SYPHILIS

Introduction This is another chapter which we may justifiably hope and expect to become obsolete during the next generation since already great progress in the reduction of cardiovascular syphilis has been actually demonstrated to the author and his contemporaries during the past generation by means of the prevention of syphilis itself in the first place its earlier recognition and more adequate initial treatment in the second place and its better therapy even in its later or tertiary phase in the third place

In every chapter that has preceded the present one a considerable revision has been necessary as the result of the rapid strides of medical progress in the past seven years since the last edition of this book Even more dramatically has progress been *made in the subject of the present chapter* in the way of preventive medicine And yet despite this advance syphilis continues to be after rheumatism the second most common and important cause of infectious cardiovascular disease By the time the diagnosis of cardiovascular syphilis is made it is in most cases a very serious condition Fortunately however it is a preventable disease and already in many parts of the world it is on the wane *and no longer common In New England two decades ago it was found* to make up 4 per cent of a large series of cases of cardiovascular disease (White and Jones 1928) being more frequent in general hospital practice than in private practice now however it makes up less than a quarter of that figure (that is less than 1 per cent) Among the Negroes in the southern part of the United States on the other hand it is still a common though decreasing cause of cardiovascular disability and death being a prime factor in about 20 per cent of cardiac patients even there it is less frequent than the factor of hypertension In a series of 414 Negroes in Texas with cardiovascular disease over twenty years ago syphilis was the chief factor in 32 per cent and hypertension in 50 per cent (Stone and Vanzant 1927) there too however the recent public health campaign gives promise of a reduction in cardiovascular syphilis, such as has occurred elsewhere

It is a very interesting fact as yet unexplained that syphilis damages the

aorta more than other arteries or the myocardium Cardiovascular syphilis consists primarily therefore of aortitis with or without secondary effects on the heart infrequently it means myocardial disease or involvement of great vessels other than the aorta such as the femoral carotid and pulmonary arteries

In a series of 50 000 consecutive autopsies in Minnesota over a period of thirty seven years beginning in 1910 syphilitic heart disease not including uncomplicated aortitis dropped in incidence from a maximum of 2 04 per cent at the beginning to 0 23 per cent at the end in individuals 40 years of age or older (Clawson 1950) the general incidence of syphilitic cardiac deaths (0 83 per cent) in this autopsy material is now less than that of deaths from calcific aortic valvular disease (1 3 per cent) Syphilitic aortic insufficiency ranked first in the manner of death in Clawson s series of cases of syphilitic heart disease (58 5 per cent) Deaths due to rupture of a syphilitic aneurysm were second with 21 per cent and those due to narrowing of the coronary orifices third with 18 9 per cent There were relatively few cases of gumma of the myocardium

In a series of 9 807 necropsies in Italy the incidence of heart disease due to syphilis was found to be 2 per cent (Venzoni 1939) in a Cincinnati hospital with a large proportion of Negro inmates however the incidence of syphilitic aortitis in autopsies from 1926 to 1937 inclusive was reported to be much higher (at least 9 1 per cent) (Gelperin 1940) while in the Philadelphia General Hospital the percentage dropped from 9 2 in the years 1927 to 1930 to 5 6 in 1935 to 1937 (there was a majority of Negro cases) (Welty 1939)

Etiology *Cause* The organism responsible for cardiovascular syphilis the Treponema pallidum was discovered in a diseased aorta in 1906 (Reuter) but long before the discovery of the actual causative agent in syphilis the connection between that disease and aortitis was known and for several centuries the production of aneurysms by syphilis was suspected (Pare 1575 Lancisi 1724, and Morgagni 1761) Gummata long known to be of syphilitic origin were early found in the heart itself

Although it is probable that the spirochete of syphilis invades the heart and aorta early in the disease at the same time that it invades other organs actual disease of aorta and of heart due to syphilis is as a rule first demonstrable either by symptoms or by signs only a good many years after the primary lesion (chancre) Twenty years elapse on the average between the onset of the infection and its evident involvement of the cardiovascular apparatus but there are wide variations the intervals ranging from a few weeks to 30 or 40 years Except in rare cases clear evidence is wanting that there is any important involvement of the heart or aorta during the primary or secondary stage (that is during the first few weeks or months) of the syphilitic infection most reports to the contrary are unsatisfactory Years ago because of the lateness of this evidence of infection aortitis and aneurysms were classed along with tabes dorsalis and general paresis as fourth stage or parasyphilitic lesions

that is the end result of the infection that had become inactive while gummata when they were found were considered manifestations of the tertiary stage still active Now we know that all these processes are but different evidences of the syphilitic infection appearing late but still active, a few aneurysms are relatively inactive scarred lesions but such unprogressive aneurysms are uncommon

There is obviously some sort of affinity between the treponema and the aortic wall just as there is between this organism and the central nervous system in certain individuals, what it is we do not yet know Most cases of acquired syphilis do not however develop cardiovascular disease at least 90 per cent never show clinical or pathologic evidence of such involvement.

Congenital syphilis as well as acquired syphilis may cause cardiovascular disease but the congenital syphilitic type is not common The simple presence of treponemata in the heart muscle of a syphilitic fetus or child (a common finding at postmortem examination) does not constitute syphilitic heart disease there must be appreciable tissue reaction or destruction in *addition* This is well illustrated by a report of a study of 939 children with congenital syphilis (McCulloch 1930) 498 of these children were over two years of age and only 5 showed any signs of cardiovascular disease and in them such heart disease was clearly of rheumatic nature of the other 441 children who were under two years of age 32 died but only 3 of these were found to have syphilitic heart disease while none of the 409 survivors showed any signs whatsoever of cardiovascular syphilis

Age Because of the possibility of cardiovascular involvement by syphilis in fetal life and of the possible acquisition of the infection relatively late in life the age at which cardiovascular syphilis may show itself clinically or at autopsy varies from birth to old age The usual age of clinical manifestation however is in the late forties the large majority of cases come to notice between the ages of 40 and 55 years In one series of 95 cases there was one patient less than 10 years old there were four between the ages of 20 and 30 eleven between 30 and 40 twenty five between 40 and 50 thirty three between 50 and 60 twenty between 60 and 70 and one over 70 (White and Jones 1928) Among Negroes the age at which cardiovascular syphilis becomes evident is younger nearer 40 than 50 frequently in the thirties and even rarely in the twenties In recent years two more cases with syphilitic thoracic aneurysms who were under the age of 30 years have been reported (Evans 1941)

Sex The male sex has far more cardiovascular syphilis than has the female In the series of 95 cases mentioned above 78 were male and 17 were female a ratio of almost 5 to 1 (White and Jones 1928) In another series of 70 cases the ratio was 6 to 1 (Nichols 1940) In Moore s series the ratio was about 2 to 1 (Moore et al 1932) and in a more recent series of 199 cases of syphilitic aortitis found among 9 807 necropsies (Venzoni 1939) there were 164 men and 34 women (5 to 1) This is undoubtedly due largely

to the far greater male exposure to syphilis and to the factor of greater physical activity

Other factors Other known etiologic factors in cardiovascular syphilis are *race* and *social and economic status* These are very important since the members of most of the less civilized races are far more subject to syphilis once it is introduced among them than are those of civilized races where social customs and measures of prevention and early treatment afford at least a certain amount of protection Even in a civilized community the percentage of cardiovascular syphilis is greater among the inhabitants of lower social and economic order In Moore s series it was about twice as common in Negro as in white patients (Moore et al 1932) A large percentage of the population of some half civilized peoples is found to be infected with syphilis what percentage of those develop cardiovascular disease due to this infection we do not know because of the lack of accurate statistics we might at first thought believe that cardiovascular syphilis would be very common in such peoples but that is not always the case as found out in Arabia by Paul Harrison (personal communication 1940) who encountered only very rare cases of aortic aneurysm or aortic regurgitation in an active medical service over many years in a country riddled with syphilis It seems likely that a relative immunity so far as serious effects are concerned can be acquired in countries where syphilis has long been almost universal and but little treated In Uganda however cardiovascular syphilis is said to be common comprising over half of all heart disease among Africans (Williams 1938)

The more laborious occupations are also almost certainly a cause for early appearance and rapid evolution of aortic changes due to syphilis because of the greater physical strain produced thereby

The factor of early and satisfactory treatment of the original syphilitic infection is undoubtedly one of much importance as it concerns the later development of cardiovascular disease of syphilitic origin in civilized com munities at least This is only now becoming evident since it is only in recent years that antisyphilitic therapy has been planned and administered in any satisfactory degree to the majority of patients An example of this effect is the decrease in the incidence of cardiovascular syphilis both relatively and absolutely seen at the Massachusetts General Hospital in recent years In 1914 Cabot reported 12 per cent of a group of 600 cardiac cases as due primarily to syphilis in 1928 White and Jones reported 5 per cent of a series of 880 cardiac cases as primarily or secondarily of this type in the same clinic while in 1949 we have found only 1 5 per cent among 1 000 cardiac cases another interesting comparison in this hospital is that of the incidence of the diagnosis of aneurysm of the aorta in the ten year period of 1900 to 1909 inclusive (113 among 51 875 cases or 0 2 per cent) with that in the ten year period of 1925 to 1934 inclusive (only 61 among 75 184 cases or 0 08 per cent despite the improved roentgenologic facilities for diagnosis) In Baltimore in 1932 Moore and his associates stated that not one of 117 patients with

early syphilis who received three or more courses of arsphenamine and treatment with mercury during periods between the courses presented any evidence of cardiovascular involvement during the period of observation (up to nine years after the infection) while 24 of 285 patients followed during this same period of observation who had received less than this amount of treatment were observed to acquire syphilitic aortitis aneurysm or aortic regurgitation Adequate treatment for early syphilis almost certainly protects the majority of patients so treated against subsequent cardiovascular syphilis Various procedures are now in progress in the use of penicillin in the rapid treatment of early syphilis for example 600 000 units of procaine penicillin daily for ten days (Kossmann personal communication 1949)

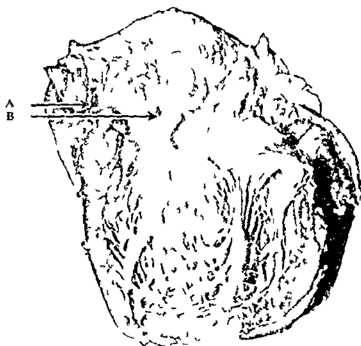


FIG 89 Photograph showing syphilitic aortitis with marked narrowing of the mouth of the right coronary artery (*B*) the mouth of the left coronary artery (*A*) is slightly narrowed Compare this with Figure 14? (Jores *Arterien* Courtesy of Julius Springer Berlin)

Pathology Cardiovascular disease due to syphilis is of three main types

1 The first and commonest type is the result of *destruction of the media of arteries* The exact pathogenesis of this lesion is not known in the aorta it is thought to result from obliterative endarteritis of the vasa vasorum It is most evident in the ascending portion of the aorta where the intima becomes pale and wrinkled due to the destruction of the media below it (Figure 89) The aortic wall is thus seriously weakened and loses its elasticity stretches and dilates The intima is thickened becomes atheromatous and may ulcerate

though ulceration is less common than in the case of primary atheroma The spirochete of syphilis may sometimes be found in the diseased aorta

Three important developments of this destructive syphilitic aortic process may occur if no one of these is found as sometimes happens the condition then remains clinically unimportant These three developments are. (1) a stretching of the aortic wall to give rise either to a diffuse or spindle shaped dilatation or aneurysm or locally to a saccular aneurysm (2) an involvement of the aortic valve to deform it and to cause aortic regurgitation and (3) a narrowing of the mouths of important branches of the aorta by an extension of the process itself

(a) *Aortic aneurysms* like syphilitic aortitis itself most commonly involve the ascending portion of the aorta less often the aortic arch and least often the descending portion in thorax or in abdomen They are only an occasional accompaniment of aortitis being found in 10 per cent or fewer of the cases but they are serious because of the pressure they often exert on surrounding structures and because of their tendency to rupture into pleural cavities pericardial sac bronchi or trachea esophagus mediastinum or even into other great vessels (pulmonary artery or superior vena cava) Aneurysms are still rarer accompaniments of other conditions such as atherosclerosis senile ectasia trauma or bacterial endarteritis They are discussed further in Chapter 28 of this book

(b) *Aortic valve disease with regurgitation* is a much more common accompaniment of syphilitic aortitis than is aneurysm occurring in one quarter to one half of the cases diagnosed clinically though rarely early in the disease It was found in 36 5 per cent of the 126 cases of syphilitic aortitis examined post mortem by Clawson and Bell (1927) and in 27 per cent of the series of cases of cardiovascular syphilis of Moore and his associates (1932) which in turn made up 10 per cent of a clinical series of 6 420 patients with various forms of late syphilis It is due to a downward extension of the aortitis to involve primarily the commissures of the valve The inflammatory process widens the commissures and by separating the cusps produces re gurgitation (Figure 131 shown on page 686) this is the reverse of the rheu matic effect which unites the cusps at the commissures to cause stenosis rather than regurgitation Extension of the syphilitic process may further damage the valve cusps themselves and cause their retraction or adhesion to the sinuses of Valsalva A very interesting finding is a rather rare eventration of one of the aortic valve cusps giving rise to a striking loud high pitched musical aortic diastolic murmur with thrill (Bellet et al 1939 Nichols 1940) A weakening of the aortic valve ring with stretching often comes with aortitis and is probably more commonly the cause of aortic regurgitation than is valve deformity per se Thus aortic regurgitation so frequently complicating syphilitic aortitis may result either from this stretching alone or from damage to the valve or from both factors The other heart valves are not affected by the syphilitic process directly except as the anterior cusp of the mitral valve may be somewhat involved or deformed by spread of the inflammatory

reaction down over it from the aortic valve or by retraction of the damaged aortic valve

(c) *Narrowing of the mouths of the branches of the thoracic aorta* by the inflammatory syphilitic process is an important and not infrequent complication of the aortitis It may even advance to the stage of actual occlusion *Coronary involvement of this nature* (Figure 89) *is particularly serious* and accounts in large part for the angina pectoris and especially for the sudden death so often occurring in patients with syphilitic aortitis It was found in 25 per cent of the series of 126 autopsied cases of syphilitic aortitis of Clawson and Bell (1927) and in over half (105 out of 199) of the autopsied cases of Venzoni (1939) Although the coronary arteries beyond their mouths are usually not involved in the process they may rarely be the seat of a syphilitic mesarteritis with narrowing and obstruction or even aneurysmal dilatation (Seydel 1935) Other arteries—the innominate carotid subclavian and intercostal—may also be more or less occluded at their mouths in syphilitic aortitis especially if there be in addition aneurysmal dilatation which compresses these arteries Such obstruction may lead to decrease and delay of one or both of the carotid or radial pulses and rarely to their obliteration with development of a collateral circulation to head or arms

Other arteries besides the aorta and coronary arteries may be attacked by the syphilitic process with thickening of wall thrombosis and occlusion or with stretching of the weakened wall and aneurysmal development There may be aneurysms anywhere in the body In themselves aneurysms exert little or no strain on the heart the strain comes if they perforate into veins (arteriovenous aneurysm) or if in the case of the aorta the coronary arteries are obstructed or the aortic valve is deformed Sclerosis of the pulmonary artery and its branches following syphilitic involvement of the bronchi and causing right ventricular failure and marked cyanosis (black cardiacs) was described in 1901 (Ayerza as quoted by Arrilaga in 1912—see bibliography of Chapter 20) but such a syphilitic sequela is excessively rare the great majority of cases of cor pulmonale with right heart failure and marked cyanosis are not syphilitic (see Chapter 20)

2 The second type of syphilitic involvement after that of the arteries is a *diffuse inflammatory reaction in the myocardium* with the presence of spirochetes (Warthin 1925 Magill 1935) Some cases of sudden death have shown this syphilitic myocarditis, but it is an infrequent manifestation of cardiovascular syphilis Rupture of a papillary muscle due to syphilitic myocarditis has been noted but it is exceedingly rare

3 The third type of cardiovascular syphilis is also rare and consists of the *invasion of the heart by gummata* These localized reactions to the presence of spirochetes may be situated anywhere in the heart—atrial walls ventricular walls or septum If they occur high in the interventricular septum they may involve the specialized conduction system of the heart—the atrioventricular bundle of His or its branches—and produce heart block of one type or another Gummata in the myocardium were found in only 3 of the 126

autopsied cases of Clawson and Bell's series (1927) Myxoid formations in the myocardium consisting of rounded translucid nodules have also been reported as a syphilitic lesion (Warthin 1916)

Symptoms Cardiovascular syphilis is often symptomless not only in its early stages but sometimes even when it has become far advanced It produces symptoms chiefly (1) by its involvement of the aortic valve which causes heart strain and eventual failure or (2) by its narrowing of the coronary artery mouths or walls to cause angina pectoris and even very rarely acute myocardial infarction (Burch and Winsor 1942) or (3) by the pressure of aneurysmal dilatation on surrounding tissue to cause pain or to obstruct blood flow in other vessels to block esophagus or air passages or to occasion hoarseness by involvement of the recurrent laryngeal nerve with paralysis The aortitis itself is almost always symptomless but sometimes a more or less constant dull ache high under the sternum has been ascribed to it even though there be no definite aneurysm

The earliest and commonest symptoms associated with cardiovascular syphilis which usually means aortitis are less commonly angina pectoris and more commonly paroxysmal dyspnea with or without cardiac asthma or frank pulmonary edema Either one or both may be present with no other symptoms at all or all the symptoms of congestive failure—more or less constant dyspnea weakness and pulmonary and systemic edema—may supervene to replace the angina pectoris or to appear at the very onset of evident trouble Sometimes pallor and loss of strength and weight also appear early in the disease

Sudden death is quite common in cardiovascular syphilis with or without preceding symptoms it was reported as having occurred in 39 of the 199 cases (20 per cent) in the series of Venzoni (1939)

Signs There may be no signs whatsoever of cardiovascular syphilis by any method of examination and the condition may be discovered only at postmortem examination Dilatation of the aorta which occurs after the process has advanced considerably may also escape attention for some time even after symptoms have appeared unless careful roentgenologic study is made Even when careful roentgenologic examination is carried out it is not possible to recognize early or slight syphilitic aortitis thereby for aortic dilata tion and secondary calcification are after all rather late effects and actual dilatation of the first few centimeters of the aorta (a common site of syphilitic aortitis) may be present with no evidence by roentgen ray because the aortic shadow at its root is buried in that of the heart in all roentgenologic views and positions as carried out routinely However by the injection of a contrast medium such as Diodrast the root of the aorta can usually be delineated in doubtful cases

Later on when the process has become extensive and has advanced to the stage of aneurysmal formation of aortic regurgitation or of coronary ob struction ordinary methods of clinical examination may reveal it but by that time the situation may be hopeless Keen observation and careful study must

always be carried out when there is a suspicion of aortitis Since symptoms and signs often appear only when the disease is advanced however it will rarely be possible to pick up the early cases in spite of routine periodic examinations Routine examinations nevertheless especially of those individuals with a history of syphilitic infection, will sometimes reveal trouble that may be amenable to treatment before any symptoms have forced the patient to consult medical advice the value of these examinations should be universally realized

With aortitis alone or with aortic aneurysm without aortic regurgitation or coronary obstruction the heart remains normal in size without murmurs but when aortic valve disease develops with increasing regurgitation the heart enlarges rapidly and may eventually increase to enormous size to produce the typical *cor bovinum* With a considerable valve defect a loud aortic diastolic murmur develops louder than is found as a rule in rheumatic aortic valve disease and often heard best at the right of the upper sternum a moderate to loud aortic systolic murmur also is usually heard there (due to the aortic dilatation) the heart sounds are masked a functional mitral diastolic murmur (Austin Flint) is common and the peripheral pulse becomes water hammer in character along with the appearance of the so called capillary pulse Stenosis does not complicate the aortic regurgitation of syphilitic aortitis although aortic stenosis probably of rheumatic origin has been encountered along with syphilitic aortitis (for example three such cases noted by Cabot 1926) A curious loud high pitched musical character may be imparted to the aortic diastolic murmur with development of a palpable thrill when as already noted above there is an eventration of one of the valve cusps (Bellet et al 1939 Nichols 1940) It is to be remembered that the aortic regurgitation of syphilitic aortitis may begin gradually and at first may be but slight hence it is possible in some cases to find only a slight to moderate aortic diastolic murmur without a Corrigan pulse

There are three signs that have sometimes been adduced as evidence of early syphilitic aortitis before the development of aortic regurgitation or of well marked aortic dilatation they are (1) an aortic systolic murmur, (2) accentuation of or a tympanitic or metallic note to the aortic second sound and (3) increased retrosternal percussion dullness These signs are all very unreliable the first two being much more common in cases of aortic sclerosis with past or present hypertension and the third being found only when there is marked aortic dilatation or a widening of or disease in the mediastinum

The *serum reaction* for syphilis (Wassermann Kahn Hinton) is generally positive and strongly so in cardiovascular syphilis sometimes in approximately 15 per cent of the cases it is negative the Hinton reaction is more sensitive than the Wassermann test It must be remembered however that syphilis with a positive Wassermann reaction may be present as an incidental infection complicating chronic valvular disease or angina pectoris which is not of syphilitic origin this fact accounts I believe for a gross overestimation of

syphilitic aortitis as a cause of angina pectoris in some parts of the world in days gone by

The essential evidence of syphilitic aortitis is most commonly presented by roentgen ray examination the bulging of the thoracic aorta (especially the ascending portion and the arch) without other adequate reason (for example hypertension) affords the essential clue (Figure 146 page 770) The electrocardiogram remains normal until the heart enlarges as the result of aortic regurgitation with the development then of the pattern of left ventricular hypertrophy and dilatation (see Chapter 9) or until the coronary circulation is interfered with when one of the many patterns of coronary heart disease may appear

Course and prognosis The onset of cardiovascular syphilis is very slow and insidious When aortitis has becomes established years after the initial lesion and has come to light because of the symptoms or signs it has produced the course is often difficult and the prognosis is often poor Sometimes however treatment helps a good deal in relieving symptoms and in retarding the progress of the disease Spontaneous cures or rather cessation of symptoms without further development of signs are also seen Not infrequently in the course of a few months to several years after the discovery of the trouble death occurs suddenly with or without preceding angina pectoris or it may result from congestive heart failure some complicating infection or cerebral lesion or rarely rupture of an aneurysm Sometimes death comes quickly even in a few weeks sometimes it is postponed for ten to twenty or more years The average duration of life from diagnosis to death used to be about three years it has been increasing steadily since more effective therapy has been carried out One of the most important factors of all in controlling prognosis is the degree of physical activity of the patient the more strenuous the life in this respect the shorter it will be a relatively quiet existence undoubtedly prolonging life This fact is a prime reason for the very serious prognosis of cardiovascular syphilis among the Negro laborers Of 124 cases of syphilitic aortic regurgitation followed personally by Blackford 57 died within one year of the discovery of the lesion 27 more died during the next two years 17 were known to be alive after three years and 8 were still alive after five years (Blackford personal communication 1936) In all probability the factor of hard physical work is more important than that of race in this regard although it is true that the relative neglect of treatment may enter also

The effect of energetic specific treatment even of this late syphilis of aorta and heart on prognosis has been in the main distinctly favorably as has been demonstrated by a number of authorities (Moore et al 1932 Padget and Moore 1935 Buch 1945 Webster and Reader 1948) A study of 116 patients (103 men and 63 women) with late syphilitic cardiovascular lesions showed the following relative survival periods for well treated moderately treated and poorly treated cases 71 months 57 months and 16 months respectively (Buch 1945) Webster and Reader studied the microscopic

sections of the aortas of 45 patients with gross evidence of syphilitic aortitis at postmortem examination with relation to the effect of treatment The patients were divided into untreated inadequately treated and adequately treated groups the criterion of adequate treatment being a minimum of at least 20 arsenical and 20 bismuth injections, only three of 19 patients adequately treated showed any activity of the process while all 9 untreated cases showed active cellular infiltration of the aorta

Sudden death *is occasionally the result of an undiagnosed syphilitic involvement* of aorta or heart without previous symptoms or signs The medical examiner or coroner establishes the cause of death If such cases were added to those in whom the diagnosis has been made before death the statistics of the total number of cases of cardiovascular syphilis in the community would be slightly increased but probably by not more than a very few per cent at most depending of course on the thoroughness of medical examination and care and of postmortem examinations in that particular community

The prognosis may be made worse in rare cases by too vigorous therapy Heart failure and even death have followed directly in a few cases from overzealous efforts to cure

Complications The important complications of cardiovascular syphilis have already been referred to under the heading of pathology—aneurysms angina pectoris coronary occlusion (not coronary thrombosis) and congestive heart failure Other types of heart disease or of vascular disease may be present in particular arteriosclerosis of aorta or of coronary arteries chronic rheumatic valvular disease hypertension and uncommonly subacute bacterial endocarditis A confusing picture is sometimes presented by the aorta when syphilis and atheroma are present together this not infrequently happens in older patients Syphilitic aortitis predisposes to sclerosis elongation and tortuosity of the aorta but apparently not much to dissecting aneurysms Pericarditis is a rare complication of aortitis and is not a part of the syphilitic picture Important cardiac arrhythmias are also uncommon especially atrial fibrillation Premature beats are occasionally seen and are frequently followed by pulsus alternans if the left ventricle is weak Heart block either *atrioventricular or intraventricular in type is found now and then but it is* rarely of high grade complete atrioventricular block and bundle branch block are much more commonly the result of nonsyphilitic coronary disease

Central nervous system syphilis complicates cardiovascular syphilis in from 20 to 30 per cent of the cases while cardiovascular syphilis has been reported in 20 to 25 per cent of cases of general paresis and in from 15 to 50 per cent of cases of tabes dorsalis

Treatment With the advent of penicillin the discussion of the treatment of cardiovascular syphilis needs radical revision It resembles that of subacute bacterial endocarditis in that a really specific and curative therapy of the active disease process has been introduced though leaving behind it as in the case of subacute bacterial endocarditis too a scarred heart but it differed markedly in the past in that there already existed for cardiovascular syphilis

reasonably good therapy Although penicillin may eventually completely replace the heavy metals namely arsenic bismuth and mercury in the treatment both of syphilis initially and of its sequel of cardiovascular disease I shall retain here for use even if only supplementary and for historic interest during transition much of the detail of the therapy presented in the last edition of this book

Current experience has established the value and safety of penicillin therapy of cardiovascular syphilis and therefore such treatment is more and more replacing that with the heavy metals At first it was feared that the speedy resolution of the active disease in aorta and heart might have serious consequences in the way of weakening the wall and of inducing the Jarisch Herxheimer reaction Hence at first very small doses of penicillin were administered for example, 500 to 3 000 units but as time went on it was discovered that much larger amounts could be safely and effectively given 25 000 to 100 000 units (Tucker and Farmer 1947 Moore et al 1948 Kossmann and Flaum 1948 Porter 1948) But apparently the coexistence of neurosyphilis especially general paresis does increase the threat of the Herxheimer reaction (Moore et al 1948) Several authorities have recommended for the adequate treatment of cardiovascular syphilis a total dosage of from 5 000 000 to 15 000 000 units of sodium penicillin given in aqueous solution by intramuscular injection over a period of about three weeks for example 40 000 units every three hours for 150 doses (Kossmann and Flaum 1948) Procaine penicillin in the dosage of 600 000 units once daily in the buttocks or 300 000 units twice daily for ten days to two weeks can be more conveniently administered

For particular symptoms special treatment is indicated as in the use of the nitrites for angina pectoris or digitalis and if necessary diuretics for congestive failure and of hypnotics and narcotics for insomnia and aneurysmal pressure pains For intractable angina pectoris and pains due to pressure or erosion by an aneurysm paravertebral sympathectomy or alcohol injection has proved of much value (see Chapter 21) Total thyroidectomy is contraindicated

It is regarding specific antisyphilitic therapy with the heavy metals that there was much disagreement in the past Some were for forcing it vigorously in the hope of stopping the progress of the disease others would give none for fear of weakening the aortic wall or myocardium by too rapid a destruction of treponemata and resolution of inflammatory tissue with resultant heart failure or increased stretching of aortic wall The wisest course undoubtedly rested between these two extremes—namely the careful long-continued administration of a moderate amount of antisyphilitic drugs determined in each individual case by the condition and needs of that case In the presence of congestive failure antisyphilitic therapy was withheld until treatment of the failure had been successful but today penicillin can be given concurrently under careful supervision

The technic in the use of the heavy metals which has been successful in

many cases of cardiovascular syphilis in the past may best be quoted directly from the several paragraphs concerned in the last edition (1944) of this book The only debatable point concerns the addition of potassium iodide which although traditional has been omitted by a number of authorities without detracting from the success of the treatment Incidentally it has not been necessary to add potassium iodide to penicillin in the new therapy of syphilis It seems reasonable therefore to place in brackets the reference to potassium iodide in the quoted paragraphs

The following procedures for the administration of specific therapy in cardiovascular syphilis although by no means the only methods that may be employed have proved by extensive experience to be satisfactory If the diagnosis is certain or reasonably sure and congestive failure or serious renal and hepatic disease are not present therapy is begun with mercury or preferably bismuth and potassium iodide It is preferable to begin with bismuth in the form of an insoluble salt (the subsalicylate) by intramuscular injection in the dosage of 0 1 gram (1½ grains) every four days for four weeks and then 0 2 gram (3 grains) weekly for another eight weeks [Simultaneously with the bismuth potassium iodide should be given by mouth 2 0 to 3 0 grams (30 to 45 grains) three times daily] Th drugs must be decreased in dosage or stopped if toxic symptoms arise such toxic symptoms consist chiefly of salivation in the case of bismuth [and of urticaria, erythema lachrymation and coryza in the case of potassium iodide] Also there must be a pause in the specific antisyphilitic therapy if congestive heart failure supervenes except that either of the two excellent mercury diuretics Salyrgan (Mersalyl) or Mercupurin (Novurit) may be injected intravenously or intramuscularly in the dosage of 2 cc weekly or once every few days until the congestion is cleared up such therapy acts however in combating the heart failure rather than in controlling the cardiovascular syphilis

At the end of this first course of twelve weeks arsenic should be cautiously added to the therapy if the condition of the patient warrants as it usually does Mapharsen in twelve weekly intravenous injections beginning with 0 02 gram and increasing gradually to a maximum dose of 0 04 gram is desirable if possible Bismarsen (bismuth arsphenamine sulphonate) may be given instead of Mapharsen to the less favorable that is the sicker patients by intramuscular injection of 0 1 gram every five days increasing to 0 2 gram at a dose for a period of twelve weeks

At the end of this second course one should return without pause to the therapy used in the first course injections of an insoluble bismuth salt [along with potassium iodide] These two courses should then be alternated every three months for a minimum period of two years After that one course of bismuth followed by one course of Mapharsen or Bismarsen should be given annually for the duration of the patient s life

Such antisyphilitic therapy as has been outlined above may now and then yield striking results with decrease or disappearance of angina pectoris or of heart block or with cessation of growth or even decrease in size of aorta or aneurysm In many cases it merely retards the progress of the disease Rarely it does harm but discrimination in the selection and administration of the therapy obviates almost all danger Taking everything into consideration prolonged but not rapid specific

therapy of cardiovascular syphilis is well worth while Not only is life prolonged by adequate therapy (by several years in Moore s series of cases of aortic aneurysm and syphilitic aortic regurgitation as compared with control cases—Moore et al 1932 and Padget and Moore 1935) but symptoms are decreased and disability is lessened

The most important consideration of all however with respect to cardio vascular syphilis is that it is a preventable disease early and thorough treatment of the initial syphilitic infection should practically wipe out syphilitic aortitis and its sequelæ

Differential diagnosis Cardiovascular syphilis chiefly in the form of aortitis is to be differentiated particularly from angina pectoris of nonsyphilitic origin from chronic valvular disease of rheumatic nature especially affecting the aortic valve from a kinked or tortuous aorta due to extensive atherosclerosis or to a high position of the diaphragm with horizontally placed heart simulating a dilated aorta in the roentgenologic anteroposterior view but easily identified in the oblique views from mediastinal tumors which may simulate aortic dilatation or aneurysm by physical examination and roentgen ray and from hypertensive arteriosclerotic heart disease with aortic dilatation aortic regurgitation and congestive failure Very rarely there may exist acute gummatous myocarditis simulating acute myocardial infarction (Reifenstein 1936) All signs and symptoms including the Wassermann and Hinton reactions must often be considered together before a definite diagnosis can be arrived at sometimes even then it is impossible to differentiate syphilitic aortitis from these other conditions The only fairly certain sign is that of the presence of an aneurysm of the thoracic aorta in the male aneurysms of the abdominal aorta are generally arteriosclerotic as are also rare thoracic aneurysms in old women The earliest stage of aortitis cannot be diagnosed clinically the aorta being at that time of normal size and shape

Aortic syphilis has been and in fact is still being overdiagnosed in the presence of the combination of angina pectoris or aortic regurgitation and of a positive serologic reaction or a history of syphilitic infection In truth angina pectoris is uncommonly due to syphilis even though syphilis is present in the case and also in some parts of the world where rheumatic heart disease is common rheumatic aortic regurgitation and syphilis with or without aortitis may be present in the same patient

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CHAPTER 17

THE HEART IN DIPHTHERIA, SCARLET FEVER, AND TUBERCULOSIS AND IN OTHER BACTERIAL INFECTIONS, INFESTATIONS, AND VIRUS DISEASES

Although this chapter is steadily shrinking in importance in the overall picture of cardiovascular disease because of current improvement in the control of infectious diseases both prophylactically and therapeutically throughout the world our knowledge of the cardiovascular effects of many diseases has widened and deepened during the last generation as in the case of the virus diseases

Two or three generations ago the bulk of all heart disease was blamed on infections many cases were rightly so labeled but many more were incorrectly diagnosed particularly those with unrecognized congenital hypertensive and coronary heart disease Now infectious cardiovascular defects are known to comprise but a minority of all cases of clinical heart disease one reason for this change in viewpoint is the actual decrease in certain serious infections that can cause primary damage to the circulation but the more significant reason is the correction of the old time exaggerated point of view It is true however that many diseases which may be fatal show changes in the heart that are terminal in nature though not present in serious degree during life and that even the infections which do not directly cause heart disease can be serious or fatal complications in cardiac cases so that their control does have an important effect on the longevity of persons with heart disease An interesting comparison of the standardized death rates per 100 000 among insured persons aged 1 to 74 years in this country in the years 1917 1941 and 1948 has recently been made possible (*Statistical Bulletin* Metropolitan Life Insurance Company March 1942 Vol 23 No 3 Dublin personal communication 1949) diphtheria in 1917 showed a rate of 21 7 in 1941 only 0 7 and 0 4 in 1948 syphilis 19 1 in 1917 9 1 in 1941 and 4 8 in 1948 pneumonia (all forms) 131 8 in 1917 23 0 in 1941 and 15 2 in 1948 typhoid

fever 12 0 in 1917 0 8 in 1941, and 0 1 in 1948 and tuberculosis (all forms) 202 2 in 1917, 40 9 in 1941 and 25 9 in 1948

Having considered in the last three chapters the more important cardiovascular infections, rheumatic acute and subacute bacterial and syphilitic we turn now to other infections which have a relatively uncommon or unimportant effect on the heart Only occasionally do a few of these infections cause serious heart disease

DIPHTHERIA

Diphtheria during and following World War II has had a recrudescence of importance because of its increased frequency in the wake of the hardships in Europe and Asia and of its protean form among the military forces of the U S A It often causes important damage to the heart muscle but happily it has been robbed of so much of its threat in recent years by large scale prevention of the disease in the first place and secondly when it does occur by the use of antitoxin that much less diphtheritic heart disease is nowadays diagnosed than was the rule a generation ago During World War II nonfaucial diphtheria was on occasion unrecognized when it attacked other parts of the body especially the skin and serious cardiac effects were at times noted before a correct diagnosis was made

Pathology The acute effect of severe diphtheria which is not quickly or sufficiently combated by antitoxin may be serious There is clear evidence that grave myocardial damage may occur and that this may lead to death The diphtheria bacillus itself is rarely encountered in the heart it acts evidently through the toxin it produces which circulating in the blood stream reaches the heart muscle The necrosis (Figure 90) produced in the myocardium may be found only at postmortem examination or it may give evidence during life by the production of various grades of atrioventricular or intraventricular block (shown by electrocardiogram) or rarely of heart failure In some cases there may be multiple small hemorrhages throughout the heart as well as in other parts of the body (as in the liver and intestines) and it seems likely that such hemorrhages in the heart muscle may play some role in the sickest cases Undoubtedly death during diphtheria results from the myocardial involvement in a considerable percentage of the fatal cases such death may come abruptly without warning or after giving evidence such as that noted above Endocarditis and pericarditis are not caused by diphtheria, except in unique cases (Sutherland and Willis 1936)

There is very infrequently any clinical evidence of a chronic effect on the heart from diphtheria even when it has been severe Survival usually means escape from any permanent or serious heart disease Slight lesions which may be discovered by microscopic examination of the myocardium doubtless occur in some cases but they are not demonstrable by clinical examination Therefore it is reasonable to infer that any serious sequelae are absent rather than present. Rare cases of chronic atrioventricular or intraventricular heart block

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but weakness and listlessness are the commonest symptoms accompanying the cardiac involvement and these may be due rather to the general effect of diphtheria on the whole body (nervous system vasomotor control and musculature) than to the cardiac involvement With the rare complication of congestive heart failure cough may appear

Signs Signs also are relatively infrequent There may appear pallor cyanosis cardiac enlargement due to dilatation tachycardia diastolic gallop rhythm (which may be due either to delayed atrioventricular conduction or to cardiac dilatation and failure or to both) an apical systolic murmur due to secondary mitral regurgitation or an arrhythmia which may include an ominous ventricular paroxysmal tachycardia and rarely bradycardia due to heart block There may be hepatic engorgement and tenderness and pulmonary rales due to heart failure If a majority of these signs are present the immediate prognosis is very serious

Fever is not a sign of diphtheritic myocardial involvement in fact the most serious heart trouble exists after the fever of the acute illness is over Fluoroscopic examination if such can be safely undertaken may show dilatation of the heart Electrocardiographic examination is of greater value than any other special method by revealing the degree of atrioventricular or intraventricular (bundle branch) block or more commonly abnormalities of the *T* wave Blood and urine examinations and other such studies are not of much help

Course and prognosis When involvement of the heart in diphtheria reveals itself by signs or symptoms the course of the illness is short and fatal or long and exhausting with the prognosis in doubt Although about half of such cases recover they are not out of danger for weeks and they may die suddenly at any time during this period of convalescence Heart block is usually a fatal sign especially bundle branch block A follow up study of cases of diphtheria at the South Department of the Boston City Hospital has revealed a few survivors after the development of atrioventricular or intraventricular block On recovery from the diphtheria such cases have lost all electrocardiographic evidence of heart block except for very rare individuals who retained some degree of atrioventricular block there were none in this particular series in whom intraventricular (bundle branch) block persisted (Faulkner and Place personal communication) though one such case was reported by Perry (1939) *T* wave changes also tend to clear up although rarely inversion of this wave in Lead 1 or Lead 2 has persisted for a few months or even a few years

Complications Heart block and cardiac dilatation have been mentioned as grave cardiovascular complications of diphtheria There are two other serious cardiovascular complications difficult to analyze namely vagal and splanchnic paralyses The tachycardia in diphtheria has sometimes been ascribed to vagal paralysis resulting from damage to this nerve by the diphtheritic toxin and also to circulatory failure from vasomotor (splanchnic) paralysis the latter has also been blamed for some of the deaths It seems

probable that these are real factors how responsible they may be as compared to actual myocarditis we do not know, it is probable that all these factors operate simultaneously in a seriously sick patient

Treatment In the first place adequate antitoxin should be given at the onset of the diphtheria, the more severe the illness the more units of antitoxin should be administered even up to 50,000 or 100 000 This early therapy is the most important of all measures to protect the heart Rest in bed should be enforced for at least several days after all signs of infection have gone even in the mildest cases and for several weeks in the severe cases especially if there have been symptoms or signs of cardiac involvement For serious cardiovascular complications absolute rest and intravenous dextrose (glucose) injections (25 to 100 cc of 50 per cent solution daily or oftener) have been found more helpful than other measures Digitalis, epinephrine (adrenaline) and other stimulating drugs with the possible exception of caffeine and theophylline ethylene diamine (aminophyllin), have been disappointingly ineffective in the treatment of cardiac failure and vasomotor collapse in diphtheria early adequate treatment of the infection itself will prevent such complications

Differential diagnosis The differential diagnosis of diphtheritic heart disease is usually not difficult It must be distinguished from the unimportant neurocirculatory asthenia (effort syndrome) that may come in diphtheria as in any infectious disease from the tachycardia due to vagal paralysis and from coincident heart disease such as rheumatic valvular disease It must be borne in mind also that diphtheria of the skin or mucous membranes other than of the fauces can result in serious heart disease

SCARLET FEVER

There is strictly speaking probably no such entity as the scarlet fever heart although there may occasionally occur temporary toxic cardiac effect Permanent heart disease certainly does however follow scarlet fever in rather rare cases Evidence that has been accumulating in the past few years indicates that scarlet fever like certain other streptococcus infections merely plays the role of an activating agent of the rheumatic infection in the heart in individuals who belong to rheumatic families (Paul Salinger and Zuger 1934 Faulkner Place and Ohler 1935) Further important evidence that scarlet fever per se does not cause any important myocardial disease has been advanced by Shookhoff and Taran (1931) who found in the electrocardiograms of fifty consecutive patients with scarlet fever only minor changes in the *T* waves or *Q T* intervals in 10 per cent and no prolongation of the *P R* interval in any case in contrast to the frequent changes especially prolongation of the *P R* interval in acute rheumatic heart disease The statistical evidence which we possess at present indicates that not over 0 5 per cent of all cases of scarlet fever are complicated by endocarditis or pericarditis or both and that a very small fraction of 1 per cent of cases of heart disease originate during scarlet fever The chronic valvular disease that results is of rheumatic type

but it does not ordinarily develop to the stage of marked valve deformity The mitral is the valve ordinarily attacked the aortic rarely In a series of 602 cases of scarlet fever observed during one year (August 1943 to August 1944) 36 (6 per cent) showed cardiac complications during the acute illness 32 with myocarditis of whom one died with atrial fibrillation and two others showed partial a v block and 4 with endocarditis (Neubauer 1945)

It is especially in patients in whom acute polyarthritis complicates scarlet fever that acute cardiac infection tends to occur valvular disease has however also been reported in scarlet fever with no arthritis It is important always to wait until the completion of convalescence before ascribing to valvular damage an apical systolic murmur which may be merely a temporary accompaniment of the scarlet fever itself More than half of the cases of acute endocarditis or pericarditis occurring in scarlet fever show an arthritis at the onset of the heart disease

The pathologic changes are similar to those of rheumatic heart disease both in the acute and in the chronic stages

There are no symptoms of the heart involvement itself except for a slight prolongation of the fever and occasionally pain from pericarditis

The only signs are the development of slight cardiac enlargement and of heart murmurs rarely the occurrence of a pericardial friction rub during or at the end of the scarlet fever and minor electrocardiographic changes noted above

The treatment of scarlet fever and therefore favoring the prevention of the infrequent heart disease that results has been improved since the introduction of penicillin which should be administered at the very onset of the hemolytic streptococcus sore throat which ushers in the scarlet fever and continued until convalescence begins in order to prevent especially the formerly serious and common complication of mastoiditis

The differential diagnosis is inconsequent in that the acute heart disease with or without pericarditis occurring during scarlet fever and the chronic valvular disease that may follow are indistinguishable from rheumatic heart disease acute and chronic

STREPTOCOCCUS HEMOLYTICUS INFECTION WITH HEMORRHAGIC NEPHRITIS

Among others Whitehill Loncope and Williams (1939) have called attention to this serious disease in childhood which is not infrequently attended by a complication of cardiac dilatation and even heart failure early in the illness (71 per cent of the series of 138 cases of Whitehill et al) but fortunately nowadays penicillin given as near the onset of the disease as possible can result in much improvement and may help to prevent the more serious cardiac effects provided the streptococcus infection itself is still active the penicillin does not cure the nephritis itself The death rate used to be fairly high (20 3 per cent of the 59 severe cases in the series just mentioned) recovery was

slow but the heart did often return to normal (see also Chapter 23) Happily the picture has changed and this disease should be on the way out

PNEUMONIA

Pneumonia either lobar or bronchial in type may prove a great strain for *an already weakened or diseased heart but it does not itself* cause serious heart disease except in rare instances when acute bacterial (generally pneumococcus) endocarditis or a septic pericarditis occurs in either case almost always a fatal complication in the days before chemotherapy with the sulfonamide drugs and the introduction of the antibiotics especially penicillin but this complication is now largely preventable and most cases that do occur are curable by the use of these drugs (formerly sulfadiazine sulfathiazole or sulfapyridine 1 to 2 gm 15 to 30 gr 3 or 4 times a day for a few days under careful observation and with blood titration and now preferably procaine penicillin by intramuscular injection 300 000 units daily for a few days to a week or terramycin chloromycetin, or aureomycin by mouth about 500 mg every 6 hours for a week) The various antibiotics should be appraised as to their efficacy by direct testing on the growth of the responsible organisms themselves

Electrocardiograms in the course of and immediately following severe pneumonia may show various arrhythmias and sometimes important changes such as inversion of the *T* waves and prolongation of the *P R* interval the more severe the disease the more marked the changes but these abnormalities subside during convalescence Undoubtedly they are to be ascribed to a direct toxic effect on the myocardium (Cohn and Jamieson 1917 Master et al 1931) At postmortem examination the heart muscle cells may show cloudy swelling but such a finding does not constitute real heart disease

As will be observed concerning typhoid fever and exanthematic typhus the weakness and collapse due to pneumonia are not the result of cardiac failure but of the infection It is therefore not to be expected that routine digitalis therapy in pneumonia should help except when there is obvious congestive failure or a rare complication such as atrial fibrillation or atrial flutter

TYPHOID FEVER

The rare invasion of the endocardium by the typhoid bacillus producing acute or subacute bacterial endocarditis has already been mentioned (Chapter 15) Much more common but of little or no clinical importance is the finding at postmortem examination of slight to moderate scattered toxic changes of muscle fibers and interstitial tissue consisting of cloudy swelling and infiltration with small round cells in the majority of cases dying of typhoid fever Also periarteritis and endarteritis have been found in the blood vessels of such patients even to the extent of causing ulceration and aneurysm of the aorta *Pericarditis is a rare complication*

Generally the heart is not affected to any important or appreciable degree

in typhoid fever Not infrequently, however *T* wave changes (flattening or inversion) and rarely delayed atrioventricular conduction can be found by electrocardiogram during the acute infection but no high degree of block (Brow 1929 Porter and Bloom 1935 Mainzer 1947) and if cardiovascular symptoms occur they are in the nature of the effort syndrome usually found in infectious disease Of course organic heart disease of other nature may happen to complicate and be overburdened by the infection but it is wrong to treat the heart with digitalis or other such drug in order to combat the symptoms of effort syndrome or of circulatory failure due to vasomotor paresis It is apparently not heart failure that kills in typhoid fever but the toxic effect with weakness and vascular collapse resulting from the infection Also avitaminosis associated with the malnutrition during a prolonged illness with typhoid fever may play a role electrocardiographically and otherwise (Rachmilewitz and Braun 1948)

TUBERCULOSIS

Tuberculosis does not cause heart disease itself except in rare cases in which there is direct tuberculous invasion of the myocardium or endocardium Pericardial tuberculosis is however occasionally encountered as either (1) an isolated lesion (2) a part of a polyserositis or (3) an extension from mediastinal tuberculosis

Tuberculosis of the myocardium is infrequently found at postmortem examination as a part of a miliary tuberculous process or in the form of a solitary tubercle or abscess It is an autopsy finding rarely even suspected during life The miliary tubercles in the heart muscle almost never produce any symptoms or signs the illness being that usually observed in miliary tuberculosis If invasion or pressure directly involves the atrioventricular conduction system heart block may occur with arrhythmia and slow pulse or myocardial tuberculosis may even cause congestive heart failure (Wilbur 1938 also personal observation 1947) Still more rare than disease of the heart muscle in miliary tuberculosis is a myocardial invasion by a solitary tubercle or tuberculous (cold) abscess such invasion is usually symptomless and without signs but it is capable of causing an aneurysm of the heart wall which may even lead to rupture and to death In a series of 7 683 cases of tuberculosis myocardial tuberculosis was found 49 times (0 63 per cent) (Raviart 1906)

Tuberculous endocarditis is also rare infrequent cases usually of miliary tuberculosis revealing at autopsy tubercles in the endocardium of the heart walls and of the valves or tuberculous ulceration of the endocardium Tubercle bacilli have been found in such endocardial lesions There is no evidence that chronic valvular disease can originate either directly from tuberculous inflammation or indirectly from the toxic effect of tuberculosis elsewhere in the body

Tuberculous pericarditis is not rare It is an important type of acute and also of chronic pericardial disease isolated or more commonly associated

with a similar involvement of pleura or with a tuberculous involvement of the mediastinum arising from lymphatic glands, spinal caries, or other cause It is not usually accompanied by myocardial or endocardial tuberculosis but in rare cases for example in miliary tuberculosis it may be thus complicated Isolated tuberculosis of the pericardium unsuspected during life has been discovered to be an occasional cause of death in elderly individuals (Thompson 1933)

Pericardial effusion is a common accompaniment of pericardial tuberculosis and may be very slow and insidious in its onset causing few or no symptoms at first but finally incapacitating the patient by its pressure effect, which prevents adequate filling of the heart (cardiac tamponade—see Chapter 27) or by associated fever and weakness The effusion often in fact usually hemorrhagic in character may develop to enormous size (even up to 2 or 3 liters) and because of its very gradual growth may be astonishingly *well supported* for a long time even for many weeks it is much better endured by the patient than is the more acute rheumatic pericardial effusion of the same amount of fluid The tuberculous effusion may be spontaneously absorbed or with the development of serious symptoms and signs require paracentesis The symptoms—dyspnea cough and oppression—come from pressure effects and but rarely include sharp pains such as are frequent in rheumatic pericarditis The signs are those of a small moderate or large accumulation of fluid in the pericardium with slight moderate or enormous increase of the area of percussion dullness over the heart and of the roentgen ray shadow With a large effusion the arterial blood pressure is low especially the pulse pressure, there is often a well marked paradoxical pulse and the systemic venous pressure is elevated with resulting prominence of the jugular veins and pulse and enlargement of the liver these are signs of acute or subacute constrictive pericarditis (the so called cardiac tamponade) A pericardial friction rub may be heard over the precordium even in the presence of a large effusion

After the subsidence of the acute process a serious chronic pericarditis may develop frequently with involvement of the mediastinum If extensive this chronic mediastinopericarditis may so cramp the heart chambers and great veins that the entrance of blood into the heart is obstructed Generally the obstruction is most manifest in the hepatic veins with resulting hepatic engorgement and ascites this condition has therefore been called chronic mediastinopericarditic pseudocirrhosis of the liver or Pick s disease (Chevers 1842 Pick 1896) but a better designation is chronic constrictive pericarditis (see Chapter 27) Sometimes the process may be slight without handicap from the nonconstricting or only slightly constricting pericardial adhesions

Tuberculosis of the blood vessels may occur in rare instances causing endarteritis granulomata and even aneurysmal dilatations The invasion may be either from the blood stream or from infected tissue (lymph nodes for example) contiguous to aorta or other blood vessel

The introduction of streptomycin has given promise of aid in a few instances of tuberculous pericarditis this drug in the dosage of 2 to 4 gm daily

has been apparently helpful but its toxic effects are a distinct drawback (see page 403 in Chapter 15)

The relationship of heart disease to tuberculosis of the lungs It has long been said that pulmonary tuberculosis is rare if there is considerable mitral stenosis This appears to be true the reason is not clear but it may be that the chronic pulmonary congestion resulting from mitral stenosis makes it difficult for the tubercle bacillus to gain a foothold In one series of 300 cases of mitral stenosis there was found but one case of pulmonary tuberculosis (0 3 per cent) and in a series of 20 000 cases of pulmonary tuberculosis there was reported to be but one case of mitral stenosis (0 005 per cent) (Montenegro 1919) Valvular heart disease of other sort (not marked mitral stenosis) is however occasionally and incidentally seen in pulmonary tuberculosis the combination was reported in 29 out of 1 097 cases of pulmonary tuberculosis valvular heart disease or both examined post mortem (Calthrop 1920) in 31 out of a series of 13 000 cases of pulmonary tuberculosis (Kellner 1921) and in 0 9 per cent of 7 115 necropsies on tuberculous patients (Brown quoted by Hawes 1932) An analysis of 522 adults with pulmonary tuberculosis revealed 3 cases of rheumatic heart disease and 2 of congenital heart disease (Buckingham and Hoffman 1935)

In contrast to the rarity of pulmonary tuberculosis in cases of pronounced mitral stenosis it is said to be rather a usual development in congenital stenosis of the pulmonary orifice (Austrian 1933) In this regard it is of interest that just the opposite conditions exist in the pulmonary circulation with these two lesions in mitral stenosis the pulmonary circulation is engorged and in pulmonary stenosis it is depleted

Much more important than the possible protective action of mitral stenosis in the case of phthisis is in rare cases the deleterious effect of extensive pulmonary tuberculosis on the heart This is not the production of the familiar so-called drop or vertical (or atrophied) heart which is sometimes seen in the more slender victims of tuberculosis with low diaphragm and general atonic state such a drop heart is of little or no importance in itself Rather is it the strain on the right ventricle resulting from increased pressure produced in the pulmonary circulation by obstruction caused by extensive destruction of pulmonary tissue fibrosis and pleural adhesions This strain may eventually in a few cases produce some right ventricular enlargement rarely to a considerable degree and not marked enough to cause definite increase beyond the normal in the percussion or roentgen ray size of the heart so that the change may easily escape notice In a very few cases actual failure of the right ventricle may occur but this is much rarer than in the case of chronic pulmonary fibrosis and emphysema of other cause which will be discussed in Chapter 20 During life there may be a great variety of size and shape of the heart shadow in the presence of active pulmonary tuberculosis (Porter and Gordon 1937)

Finally it is to be recognized that in patients with active tuberculosis in the lungs or elsewhere there is commonly as in the case of other infections

a certain degree of neurocirculatory asthenia with dyspnea palpitation and heartache which may on hasty analysis be wrongly ascribed to heart disease or to a toxic effect of tuberculosis of the heart

The course prognosis and treatment of tuberculosis of the heart and pericardium resolve themselves primarily into those of the underlying tuberculosis be it miliary pulmonary or of the nature of polyserositis The prognosis is always grave though some cases recover this number has increased somewhat since the introduction of streptomycin A pericardial effusion may need to be tapped and cases of chronic constrictive pericarditis may require surgical relief by pericardial resection Active tuberculosis of pericardium and heart must be treated by rest and good nursing care and a trial of streptomycin just as in the case of active pulmonary tuberculosis but the prognosis is always serious

EPIDEMIC CEREBROSPINAL MENINGITIS

Meningococcus infection may in rare cases involve the heart and cause an acute bacterial endocarditis or pericarditis as noted in Chapter 15 but such cardiac involvement is now largely preventable or amenable to recovery by the use of chemotherapy Meningococcic myocarditis has also been reported (Saphir 1936)

GONORRHEAL INFECTION

Acute or chronic gonorrhea may in rare cases infect the heart especially following gonorrheal arthritis or a virulent illness of other nature due to the same organism The involvement occurs in the form either of acute or of subacute bacterial endocarditis and is no longer as it once was fatal the newer chemotherapy being a specific remedy in most cases

OTHER BACTERIAL DISEASES INCLUDING SEPTIC INFECTIONS

Erysipelas septic infections and pyemia due to streptococcus or staphylococcus used to be occasional causes of acute bacterial endocarditis septic (purulent) pericarditis and myocardial abscesses Generally these were but terminal manifestations and were not responsible for death but sometimes they constituted the chief or most important part of the disease Treatment used to be of little avail when the heart itself was diseased but both prevention and recovery of cardiac and pericardial complications now may follow the use of the antibiotics (especially penicillin) and of the sulfonamide drugs aided by pericardiotomy and drainage in the case of purulent pericarditis

RICKETTSIAL DISEASES

Typhus fever Myocardial lesions and vascular disease (endarteritis) may result from exanthematic typhus fortunately now rare in civilized countries at peace they are as a rule of little or no significance Transient *T* wave ab-

normalities in the electrocardiogram are common during the acute infection (Norvut 1947) Complete arterial obstruction and gangrene may however complicate a few cases The toxicity and vasomotor paralysis resulting from this infection may kill but involvement of the heart is probably not responsible for death Endocarditis and pericarditis do not occur except from a secondary infection

Another important rickettsial disease which has been found even more constantly to be associated with myocardial involvement namely *tsutsugamushi fever* or *scrub typhus* was studied during World War II A large proportion of electrocardiograms of cases of scrub typhus has shown abnormalities chiefly in the *T* waves with recovery in most cases

Rocky Mountain spotted fever also falls into the group of rickettsial diseases and may affect the myocardium during the acute illness

VIRUS DISEASES

An interesting and important advance in our knowledge of the effect of infections on the heart has taken place during recent years in the field of the virus diseases In most instances the victims of such infections escape any serious cardiac injury but in a certain number of instances rare as a rule the myocardium may be seriously affected Virus pericarditis has also of late been identified

Influenza had long been suspected and by some so incriminated but only in the last few years has actual proof been presented (Finland et al 1945) It is quite possible that lesser lesions of the heart muscle have often resulted from influenza but serious or fatal myocarditis is rare Most of the symptoms which years ago were attributed to such a condition were characteristically those of a fatigued state or neurocirculatory asthenia which so often complicates the convalescence from any infection (see Chapter 22)

Mumps has been shown to produce temporary atrioventricular block in rare cases clearing with convalescence (Rosenberg 1945)

German measles (rubella) has been shown to have in many instances a serious effect on the eyes and heart of a fetus if it attacks the mother during the first three months of pregnancy (Gregg 1941 Swan 1943)

Yellow fever may give rise to nonspecific myocardial inflammation and degeneration in fatal cases (Cannell 1928)

Poliomyelitis Recently myocardial changes characterized by perivascular infiltration of lymphocytes and neutrophiles have been reported in 6 out of 7 cases with poliomyelitis who died suddenly during the acute or convalescent stages (Saphir and Wile 1942) and several other observers have confirmed these findings since (Gefter et al 1947 Ludden and Edwards 1948)

Infectious hepatitis and *infectious mononucleosis* have also been found to cause in some cases myocardial involvement as indicated electrocardiographically

Still other viruses need further appraisal in this respect

TRICHINIASIS

It was long known that trichiniasis may involve the myocardium as well as other muscles in the body but the possible frequency with which the trichinae invade the heart in well infested cases was not pointed out until 1935 (Spink 1935) A serious effect directly from this heart involvement itself has not been found but changes in the electrocardiogram (flattening or inversion of the *T* waves low voltage of *QRS* waves and intraventricular block) in some cases (6 of 18 patients with myocardial trichiniasis in Spink s series) may justifiably be attributed to the presence of the parasites in the heart muscle In another series of 44 cases of trichiniasis of mild type however only 2 showed possible clinical evidence of myocardial involvement (Beecher and Amidon 1938) There is no specific therapy

TRYPANOSOMIASIS

A cause of heart disease in South America (especially in Brazil) rare or nonexistent elsewhere namely cardiac trypanosomiasis has been frequently reported in recent years following its discovery in human beings by Chagas in 1909 This consists of the invasion of the myocardium in childhood by trypanosomes (Figure 91 illustration below) with foci of inflammatory reaction which later lead to cardiac weakness and failure and arrhythmias in

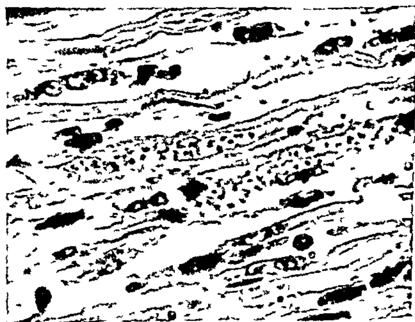


FIG 91 Microphotograph showing myocardial trypanosomiasis (Chagas disease) Note Trypanosoma cruzi near the center of the field (Kindness of Drs C Chagas and R Menezes Brazil and Frank Wilson Ann Arbor Michigan)

middle life Sudden death may result The pericardium endocardium and valves are not involved but the myocardium is said to be more often involved than in any other disease In the chronic cases multiple areas of fibrosis may be found scattered through the heart muscle Thousands of cases of this remarkable type of heart disease have been seen in Brazil but it has not yet been encountered in the United States or Europe

ECHINOCOCCUS DISEASE

Infection with the echinococcus may involve the heart and a number of cases of hydatid cysts in or attached to the walls of atria and of ventricles or interventricular septum have been reported It is usually but a part of general echinococcus disease I have encountered such cases in Greece (1948)

ACTINOMYCOSIS

Actinomycosis of heart and pericardium is a very rare infection Thirty years ago the case of a man 34 years old was reported with initial lesion in the esophagus and secondary invasion of the heart pericardium lung and pleura it was noted that twenty two other cases had been described previously (Letulle and Hufnagel 1919)

INTESTINAL PARASITES

Most of the parasites that invade the intestinal tract of man do not affect the heart these include the roundworm (ascaris) the pinworm (oxyuris) and the ordinary tapeworms (taenia saginata and taenia solium) but the hook worm (ankylostoma) and less commonly the fish tapeworm (dibothrio cephalus latus) may by their production of severe anemia cause an important degree of cardiac dilatation and loud murmurs (see Chapter 23)

OTHER INFECTIONS AND INFESTATIONS

A few other diseases may involve the heart for example Brucella meli tensis (Malta fever) sarcosporidial infection of the myocardium filariasis (with ova found in the heart) strongyloidiasis cardiac heterophydiasis (in festation with flukes from raw fish) and cysticercosis of the myocardium (and brain) In the sixteenth century there were frequent reports of worms in the chambers of the human heart before the days when it was recognized that these supposed worms were actually elongated blood clots both ante mortem and post mortem it is however true that the dog s heart may contain worms (*Dirofilaria immitis* see Query *J A M A* 1924 CIII 1728) which intro duced by insect bite go through a cycle of development and then migrate in adult life along the veins into the right heart chambers where by their accumu lation en masse the individual thread like filaria attaining the length of one to two feet, may actually block the circulation and cause pulmonary embolism

Rheumatoid arthritis periarteritis nodosa and conditions like lupus erythe-

matosus allied to these are quite frequently attended by heart disease but it is still difficult or impossible in view of our ignorance as to their etiology to label them as infections or even reactions to infections or toxic states (see Chapter 23)

FOCAL INFECTIONS

Focal infections may have a deleterious effect on the heart either directly or indirectly Actual cardiac disease of the nature of bacterial endocarditis is known to follow an acute focal infection like that of tonsil of middle ear or of skin But this happens only rarely except in the case of dental infections and extractions which almost certainly are a very important source of entry of the Streptococcus viridans into the body to inaugurate the grave infection of subacute bacterial endocarditis in cases of rheumatic or congenital heart disease (see Chapter 15) it behooves us in such cases to use the greatest vigilance in avoiding strain from too much operative work at any one time and in combating the serious results of dental and other focal infections by the use of the antibiotics (in particular penicillin) and of the sulfonamide drugs and otherwise

How frequently slight myocardial damage or a mild endocardial lesion with recovery may occur with such focal infections we do not know but there exists no proof that this is even an occasional happening We do know that heart disease already existing is sometimes aggravated by the presence of focal infections with the appearance of arrhythmia or of symptoms of congestive failure or angina pectoris or with their increase if already present Whether or not there is actual heart disease cardiac arrhythmia may be set off or aggravated by focal infections such arrhythmia is as a rule entirely unimportant in itself *consisting of premature beats (extrasystoles) or paroxysms of tachycardia* but sometimes it may comprise atrial fibrillation or flutter or prolonged paroxysmal tachycardia Among the focal infections which may precipitate or aggravate cardiac arrhythmia congestive failure or angina pectoris are chronic cholecystitis prostatitis pyelitis colitis infection of gums apical tooth abscesses frontal sinusitis lung abscesses and other similar troubles

Correction of these focal infections by surgery or by other measures (if the circulatory condition permits) may relieve the patient of his temporary state of ill health or at least cause improvement the risk of such corrective procedures is usually justified provided too much is not attempted at one time (the removal of more than one or two infected teeth at one sitting for example, may result in vasomotor shock or may itself precipitate heart failure and death) The wisest course then is to view focal infections so far as the heart is concerned neither with overmuch fear nor with excessive disregard to consider them as possible important factors producing a state of ill health which may cause strain on the heart and to eradicate them if possible and feasible However it is a mistake to perform an operation of choice and not of necessity for example to remove a symptomless gallstone (or to correct surgically a

simple inguinal hernia) in the face of severe angina pectoris or of congestive failure

INFECTIONS NOT CAUSING HEART DISEASE

Many infections never cause heart disease although they may precipitate such trouble as failure or atrial fibrillation in hearts already diseased or they may be attended by complicating infections which do cause heart disease This is particularly true of most of the contagious diseases of childhood whooping cough (pertussis) chickenpox (varicella) and measles (rubeola) The acute respiratory tract infections—rhinitis sinusitis pharyngitis laryngitis tracheitis and bronchitis—do not of themselves cause heart disease, but like tonsillitis they may occasionally precipitate the rheumatic infection which does almost always damage the heart The same statement is true of otitis media but infections of the gastrointestinal and genitourinary tracts very rarely precipitate any heart trouble

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CHAPTER 18

THE HEART IN THYROID DISEASE AND IN DISEASES OF OTHER GLANDS OF INTERNAL SECRETION

Although this chapter requires less revision since the last edition than most of the rest of the book it is like several other chapters decreasing in importance and quite likely can be eliminated altogether eventually or at least demoted to a small section in the chapter on miscellaneous etiologic relationships This is of course due to the constantly earlier recognition and more adequate treatment of endocrine diseases before the heart and blood vessels are importantly affected

Endocrinopathy has very little serious effect on the heart Even that disorder which has much more influence than any other namely thyrotoxicosis now accounts for but a small fraction of 1 per cent of cases of heart disease in any enlightened community However there are many interesting and important cardiovascular and circulatory relationships and effects of the endocrine hormones normally and abnormally For example the glands of internal secretion especially the adrenal the posterior pituitary and the thyroid have an important influence on the distribution of water throughout the body partly by a direct effect on the kidney and cell permeability in general and partly by an effect on electrolytes and metabolism of carbohydrates protein and fat The adrenal and possibly the posterior pituitary play an important role in the renal control of sodium and upon its internal distribution Transfers of sodium and potassium across cell membranes are influenced by the hormones And now the hormones are being studied as to their striking influence on the course of certain diseases such as rheumatoid arthritis and rheumatic fever A grea deal of study remains to be done on these relationships but they are opening up an important field which may as a matter of fact result eventually in a considerable revision of a book such as this Further discussions of hormonal influences will be found elsewhere in the book for example later in the present chapter in the discussion of adrenal diseases and in the chapters on rheumatic fever and congestive failure

DISEASES OF THE THYROID GLAND

Diseases of the thyroid gland which materially affect the heart are only that which produces an excessive or toxic secretion (exophthalmic goiter or Graves disease) resulting in thyrotoxicosis, and that which is attended by a markedly decreased secretion (myxedema and cretinism)

Simple enlargement of the thyroid gland (colloid or simple or endemic goiter) causes no trouble with the heart or circulation unless the gland becomes so large that pressure on veins and arteries results in embarrassment to the entrance of blood into and its exit from the heart or compression of trachea and bronchi interferes with respiration (Rose 1878 Kocher 1902) Adenomatous goiter (struma nodosa) is much more likely to cause these disturbances than is simple colloid goiter In some parts of the world for example in the north central (middle west) and northwestern regions of the United States bordering on the Great Lakes and westward to the Pacific Ocean and in Switzerland colloid or simple goiter with its occasional slight secondary circulatory embarrassment is common in other parts of the world for example in New England and in other lands bordering the sea where iodine is plentiful such goiter is rare

Excessive secretion is not produced by a colloid goiter but if later in life the simple colloid goiter becomes adenomatous thyrotoxicosis may be superimposed

THE HEART IN THYROTOXICOSIS

Thyrotoxicosis also called hyperthyroidism may result from general hyperplasia or from adenomatous goiter The term thyrotoxicosis will be used throughout the book in the place of hyperthyroidism since it indicates a toxic degree of hyperthyroidism and includes abnormal thyroid secretion if such exists as well as excessive secretion

Persistent overactivity of the thyroid gland commonly gives rise to an important but preventable type of heart trouble which has become familiarly known as the thyroid heart but which might better be called the thyrotoxic heart or the heart in thyrotoxicosis For the most part the heart as well as the circulation in general in thyrotoxicosis is simply physiologically overactive pathologic changes that is real heart disease in thyrotoxicosis is relatively rare The true thyrocardiac may be said to be the individual who as a result of thyrotoxicosis has atrial fibrillation and eventually if not properly treated cardiac enlargement and congestive heart failure as a rule the evolution of a thyrocardiac is in just that order

Frequency Thyrotoxic heart disease varies in frequency both absolutely and relatively in different parts of the world not only according to the frequency of thyrotoxicosis in such parts but also according to the rapidity of diagnosis and proper treatment of the thyrotoxicosis In New England 20 to 25 years ago thyrotoxicosis was found to be a causative factor in 3 per cent of

2 314 cases of organic heart disease (White and Jones 1928) in Virginia it was reported in 3⅓ per cent of 300 cardiac patients (Wood Jones and Kimbrough 1926) while in Oregon it was found in 11 per cent of 1 344 cardiac cases (Coffen 1929) in Oregon there is much more endemic (colloid) goiter than in New England and Virginia out of all proportion to the amount of thyrotoxicosis that is the endemic goiter is relatively much more frequent than the thyrotoxicosis That thyrotoxic heart disease is preventable and is already decreasing in communities where early diagnosis and adequate treatment of the thyrotoxicosis itself are carried out is indicated by the fact that among the first 2 500 patients whom I examined in consulting practice from 1920 to 1927 because of cardiac symptoms or signs there were 24 cases of heart disease due to thyrotoxicosis while among the next 2 500 patients seen from 1927 to 1933 there were only 10 such cases in the third lot of 2 500 private patients seen from 1933 to 1940 there were 4 cases and in the fourth such series examined from 1940 to 1946 there were but 3 thyrotoxicosis not responsible for heart disease was occasionally found throughout the entire period

Etiology *Cause* The fundamental cause of this type of heart disease is an abnormal activity of the thyroid gland with excessive (or disturbed) secretion The mechanism by which thyrotoxicosis produces heart disease is probably dependent on three factors which may be summarized briefly as follows First the increased general body metabolism which results from abnormal thyroid activity increases the demand on the heart and circulation It has been estimated that the blood flow at rest is at least 50 per cent above the normal in a case of thyrotoxicosis of average intensity and that with exercise this disproportion is still greater The increased blood flow is due not only to the increased pulse rate but also to an increase of volume output per beat from the heart although this increase of volume output per beat is less than in a normal heart responding to exercise with the same degree of tachycardia as that found in thyrotoxicosis The systolic blood pressure is somewhat elevated and the diastolic pressure often lowered so that the pulse pressure is frequently much increased This constantly increased blood flow is maintained by a constant overactivity of the circulation Such persistent overactivity tends to increase somewhat the size of the heart both in muscle (thus producing a simple work hypertrophy) and in capacity (dilatation) but cardiac enlargement is very inconstant and not the rule in the majority of cases Eventually in some very severe prolonged cases and in those complicated by valvular heart disease hypertension or coronary disease the persistent overactivity can cause excessive strain arrhythmia and failure A possible parallelism has been seen in experimental animals which show considerable cardiac enlargement after excessive exercise maintained during much of the time for weeks or months

A second and more important consideration however is that practically all thyrotoxic heart disease starts with a persistent atrial fibrillation the tachycardia and arrhythmia of atrial fibrillation add to the strain of the thyrotoxicosis and tend after some years to produce cardiac enlargement which might

not have occurred from atrial fibrillation in the case of a normal heart to start with without thyrotoxicosis particularly if the ventricular rate were adequately controlled by digitalis (an impossibility in the presence of considerable thyrotoxicosis) A third factor that helps to explain the heart disease in thyrotoxicosis is that the heart itself is the seat of specific thyroid stimulation with local increased metabolism as in the case of other tissues in the body this increased wear and tear of the cells of the myocardium favoring in its turn enlargement and failure A fourth possible factor is that of a kind of arteriovenous shunt or aneurysm with blood rushing through the widely dilated vessels of the thyroid gland affording an appreciable extra burden for the heart and favoring enlargement as in the case of a traumatic arteriovenous aneurysm anywhere (Boas 1923)

An actual myocardial lesion consisting of degenerative changes at one time suggested as an important finding, has been in more recent years discounted and shown to be but an inconstant incidental occurrence (McEachern and Rake 1931 Weller and associates 1932)

A distinction so far as the heart is concerned between general glandular hyperplasia and the so called adenomatous goiter with hyperfunction (toxic adenomata) cannot be made as a rule the latter is found in older patients in whom other causes of heart strain (such as hypertension and coronary disease) are also more likely

The frequency of definite cardiac abnormality (not simply tachycardia and cardiac symptoms) in patients with thyrotoxicosis has been reported variously from a high estimate of enlargement of the heart in 50 to 60 per cent of fatal cases (McEachern and Rake 1931 Kepler and Barnes 1932) to a low estimate of only a few per cent in unselected groups atrial fibrillation in about 15 per cent and cardiac insufficiency in 5 to 10 per cent These abnormalities of the heart are much more common when there are complicating factors like hypertension

Age The age at which thyrotoxicosis is found varies widely, from 3 years up to 76 but the commonest age of onset is from 20 to 40 years In a series of 500 cases of thyrotoxicosis analyzed by Means and Richardson (1929) the age incidence of onset by decades was as follows first decade 3 cases second 60 third 165 fourth 147 fifth 93 sixth 29 and seventh 3 The average age was 37 years in another series of 500 cases of thyrotoxicosis (Hurxthal 1928) The age incidence of thyrotoxic heart symptoms parallels this more or less closely in a series of 68 cases 56 per cent were between 30 and 50 years old (White and Jones 1928) In a series of 108 cases of thyrotoxicosis with atrial fibrillation the average age was 51 5 years (Barker Bohning and Wilson 1932) these represent the more advanced cases on the way to serious thyrotoxic heart disease

Sex In thyrotoxicosis itself the female sex predominates over the male th ratio is about 5 to 1 In Means and Richardson s series (1929) of 500 cases of thyrotoxicosis there were 417 females and 83 males But the males are more severely affected and so show a relatively higher percentage of cardiac

involvement (by about 2 to 1) in a series of 34 cases of my own of thyrotoxic heart disease there were 24 women and 10 men

Other etiologic factors Race has little to do with thyrotoxic heart disease but in days gone by social and economic status did play a role in that inadequate financial resources did at times prevent early diagnosis and surgical correction of the thyrotoxicosis and so favored the establishment of heart disease In thyrotoxicosis itself heredity plays a part how important we do not know

In the incidence of simple nontoxic goiter and perhaps secondarily in that of toxic goiter there is a role played by geographic factors involving iodine content of foods and water Heart trouble due to thyrotoxicosis is more common in regions where there is much simple goiter but this is not due to the goiter itself The change of the simple goiter later in life to adenomata which can become toxic may account for this finding

Finally the education and intelligence of both the lay and medical population determine the rapidity with which the thyrotoxicosis is detected and corrected—a factor of very great importance in the prevention of heart disease

Pathology There are no constant cardiovascular lesions in thyrotoxicosis Enlargement of the heart with hypertrophy of the fibers is present in many cases especially in those with long-established atrial fibrillation but it is sometimes difficult to exclude the factors of hypertensive and coronary heart disease in these cases In a few cases necrosis of the myocardium has been found but this finding has not been confirmed as a thyroid effect The heart weight is generally somewhat increased to 400 or 500 gm in serious cases the average weight of the hearts of 13 fatal cases was 438 gm the two heaviest hearts weighing 530 gm each (Barker Bohning and Wilson 1932) With the onset of failure dilatation of the cavities and atrioventricular valve rings occurs but endocarditis and pericarditis are not found as a primary result of thyroid toxicity

Symptoms There are no characteristic symptoms of thyrotoxic heart disease The early cardiovascular symptoms of thyrotoxicosis itself are due to the tachycardia and effort syndrome they are chiefly palpitation and dyspnea and uncommonly heartache If atrial fibrillation or failure supervenes these symptoms increase Palpitation is of two types (1) the forceful beating with normal heart rhythm which may be extremely unpleasant and (2) that due to paroxysmal changes in rhythm Periods of rapid palpitation are common in thyrotoxicosis whether or not the heart is diseased they last a few minutes to a few hours and are due to paroxysms of sinoatrial or ectopic atrial tachycardia or of atrial fibrillation or flutter Angina pectoris rarely accompanies thyrotoxicosis and then only in older persons in whom the stage is already set by the presence of coronary disease which is not sufficient in itself to give rise to the paroxysmal pain The angina pectoris like the arrhythmia and congestive failure may be relieved by thyroidectomy when the metabolic rate is reduced thereby

Signs Increased heart action both in rate and for e is the most common

cardiovascular sign in thyrotoxicosis and this activity is manifest on inspection palpation and auscultation over the precordium on inspection and palpation of the arterial pulse in neck and arms and on fluoroscopic examination Enlargement of the heart congestive failure and arrhythmia when they occur show themselves in the usual way In the early stage of the disease the heart may at first appear to be enlarged on hasty inspection and palpation because of the forceful beating against the chest wall when really it is of normal size Cardiac hypertrophy has however been found at autopsy in the majority of fatal cases (Friedberg and Sohval 1937) A harsh unusually superficial systolic murmur is sometimes heard in thyrotoxicosis in the second and third intercostal spaces just to the left of the sternum its origin is not clear but it is probably a physiologic pulmonary murmur dependent on the increased pulmonary circulation with dilatation of the pulmonary artery reinforced by the forceful heart action and thin chest wall This pulmonary systolic murmur has in rare cases been attended by a slight thrill Also at times a to and fro friction rub has been noted in the region of the pulmonary conus (Goodall 1920 Lerman and Means 1932) and in very rare cases a functional aortic regurgitant murmur has also been described (Parade 1935)

Exophthalmos and thyroid gland enlargement the most common signs of thyrotoxicosis may be but little evident in some cases and the heart action may first suggest the correct diagnosis A staring or worried look is sometimes present in the absence of frank exophthalmos lid lag may be present also with little exophthalmos Bulging of the eyes unilateral or bilateral may actually be precipitated or aggravated by thyroidectomy

In almost 80 per cent of cases of thyrotoxicosis the heart rhythm is normal and the pulse rate is fast averaging 100 to 120 per minute at rest Rare cases have a normal or only slightly elevated pulse rate In the remaining 20 per cent the heart rhythm is disturbed the disturbance consisting almost invariably of atrial fibrillation (noted in 207 of Ernstene s 1 000 cases 1938) of permanent nature in two thirds of the cases and of paroxysmal type in one third In addition there are relatively infrequent cases with atrial flutter and atrial paroxysmal tachycardia

Atrial fibrillation is commonest in the cases with congestive failure occurring in the majority of these in one series of 111 cases of thyrotoxicosis with congestive heart failure atrial fibrillation was present in 83 per cent (Hurxthal personal communication 1930) Of 232 cases of atrial fibrillation due to thyrotoxicosis Hurxthal found that 38 per cent had also congestive failure Thus atrial fibrillation may be considered to be but a stepping stone to congestive failure an argument against such an actual entity as thyroid myocardial disease since atrial fibrillation often occurs without evidence of disease in the heart muscle In Ernstene s series of 1 000 cases of hyperthyroidism 44 (4 4 per cent) had congestive heart failure the two most important factors responsible for this complication were organic heart disease and uncontrolled atrial fibrillation

The systolic blood pressure is usually somewhat elevated in thyrotoxicosis

averaging 140 to 150 mm mercury in one quarter to one third of the cases it exceeds 150 The diastolic pressure is usually at a slightly decreased level averaging 60 to 70 mm Thus the pulse pressure is generally increased and the arterial pulse is full

The roentgen ray study of the heart in thyrotoxicosis shows often considerable prominence of the pulmonary artery (probably secondary to the marked increase in the pulmonary circulation) and unusually energetic rapid heart action these two signs are together very suggestive and almost pathognomonic of thyrotoxicosis especially with the subject in the resting state In spite of overactivity however the heart sometimes appears to be lacking in tone in the presence of thyrotoxicosis Aortic regurgitation also gives markedly increased cardiac action in a young person especially but the considerable cardiac enlargement and the aortic diastolic murmur make the differentiation easy the water hammer pulse is not so good a differentiating sign for in occasional cases of thyrotoxicosis with much peripheral vasodilatation there is a well marked Corrigan pulse If cardiac enlargement is present it is best made out by roentgenologic study Arrhythmias may be seen fluoroscopically but are not so well distinguished as by electrocardiography Unusual clearness of the lung fields has been noted as occurring in thyrotoxicosis probably largely because of the thin chest walls of most of the patients

The electrocardiogram shows no specific effect of thyrotoxicosis The tachycardia and arrhythmia that may be present are readily seen but the individual complexes are otherwise normal It was thought years ago that the *T* wave might be found unusually high because in hypothyroidism the *T* wave is always low but this has proved not to be the case in fact in many cases the *T* waves are low and in rare cases may actually be inverted in Lead 2 (Graybiel and White 1935) doubtless a sympathetic nervous effect it has been shown that sympathetic stimulation contrary to early ideas lowers or inverts the *T* waves while vagus stimulation raises them (Hartwell Burrett Graybiel and White 1942)

The basal metabolic rate during the active stage of thyrotoxicosis is always high though it varies considerably with the individual case being studied A rate of 50 to 75 per cent above normal is not infrequent 25 to 30 per cent above normal is considered to be on the borderline and demands close scrutiny for signs of thyrotoxicosis It must be remembered that careful technic and avoidance of excitement are essential before judgment can be passed confidently on a borderline case or even on one that shows a distinctly high rate Also it is important that repeated basal metabolic rate determinations should all show high readings in confirmation of the diagnosis of thyrotoxicosis one or two readings in doubtful cases are inadequate Congestive heart failure alone may definitely raise the basal metabolic rate to about +30 per cent apparently as the result of increased work occasioned by the labored breathing it has been reported as high as 40 to 50 per cent above normal though such increase is unusual The pulse rate pulse pressure and blood flow are all usually increased proportionally to the rise of the basal metabolic rate Al

though operative relief or spontaneous remission of active thyrotoxicosis may occasionally leave behind some cardiac involvement especially atrial fibrillation symptoms and signs usually subside along with the metabolic rate It should be added that very rare cases of thyrotoxicosis may have basal metabolic rates within the normal range (0 to +10 per cent for example) such patients probably represent the small group of individuals who normally show low rates (−20 to −30 per cent) without myxedema Thus all evidence is necessary besides the basal metabolic rate in difficult diagnostic cases

Two more specific tests for thyrotoxicosis than the basal metabolic rate have been introduced in the past few years they consist of (1) the measurement of the protein bound iodine in the blood which should normally not exceed 7 5 to 8 0 gamma per cent and (2) the calculation of radioactive iodine (I 131) uptake by the thyroid gland which should normally not exceed 50 per cent but which in thyrotoxicosis is much increased This latter test is much more accurate than either the former or the basal metabolic rate determination

One of the most important of all diagnostic clues is the rapid and favorable response of true thyrotoxicosis to iodine therapy

Course and prognosis The course and prognosis of thyrotoxic heart disease are extremely variable and depend on the severity and duration of the thyrotoxicosis The abnormal condition of the heart may be scarcely noticeable and with the clearing up of the cause of trouble occasion no further symptoms and few or no signs With very severe thyrotoxicosis that has lasted for a long time heart disease may be evident by the presence of enlargement atrial fibrillation and congestive failure but there are infrequent exceptions when the heart may appear to be perfectly normal even after a good many years The usual case of average toxicity shows in the course of years heart changes that are more than functional if there is no operative relief or spontaneous remission death from heart failure may ensue in such cases after a few more years Of a series of 178 fatal cases of thyrotoxicosis 27 showed severe congestive failure in 9 of which no other factor could be found than the thyrotoxicosis alone (Kepler and Barnes 1932) Other complications such as pneumonia may intervene to end the story Now and again in wasted and pigmented aged individuals chronic heart disease can be traced back to a former thyrotoxic state but is very likely to be wrongly interpreted as "arteriosclerotic" if the thyrotoxicosis is still active in these cases operation or other specific therapy should be carried out and may be expected to afford considerable relief

It is to be noted that thyrotoxicosis tends to recur after subtotal thyroidectomy in about 10 per cent of the cases (Greene and Hurxthal 1941) hence the return of atrial fibrillation or other signs or symptoms during the years following operation should make one think of this possibility

Complications The commonest cardiac complication of thyrotoxicosis is atrial fibrillation which may occur at first as a functional disturbance alon

with little or no actual heart disease In the late stages of thyrotoxic heart disease congestive failure may supervene It is of much interest that in thyro toxicosis as in beriberi the cardiac output may continue to be increased well above the normal despite the presence of considerable congestive heart failure with elevated systemic venous pressure

Chronic rheumatic valvular disease is an occasional complication of thyro toxicosis and atrial fibrillation may lead to a diagnosis of one or the other condition when both are present Coronary heart disease may be another com plication in the older cases and the combination may produce angina pectoris Hypertension of high grade may also occur (in about 10 per cent of the cases) the systolic blood pressure in thyrotoxicosis itself rarely exceeds 160 mm mercury

Treatment The treatment of the heart condition resulting from thyrotoxi cosis is fourfold (1) therapy of the thyrotoxicosis (2) therapy of heart fail- ure (3) therapy of atrial fibrillation and (4) observation for recurrence of abnormal thyroid activity

The first of these therapeutic procedures namely the treatment of the thyro- toxicosis comes foremost in the consideration of almost every case because not only does this therapy control the cause of trouble but it actually may relieve without further therapy either or both of the serious complications congestive failure and absolute arrhythmia

After careful trial of other methods of treatment of active thyrotoxicosis (either ordinary exophthalmic goiter or adenomatous goiter) a good many authorities (e g Means et al personal communication 1951) still believe that the best therapy in the present state of our knowledge is subtotal thyroid ectomy Rest in bed and roentgen irradiation though they have been apparently effective in some mild cases are far less dependable in the long run and any delay of proper treatment may do harm

A useful measure in the preparation of patients for operation has been the administration of iodine for one to two weeks for example potassium iodide 5 gr (0 3 gm) once daily in saturated solution the 5 minims or grains contain ing 330± mg of iodine or Lugol s solution 10 minims (0 60 cc) containing 60 mg of iodine three times a day for ten days Iodine promotes the storage of thyroglobulin in the follicles and places a barrier in the way of escape of hormone from the gland (Lerman and Salter 1936) hence the high basal metabolic rate the fast pulse rate and all the symptoms of thyrotoxicosis are much abated and the patient is a better risk for operation Iodine therapy alone is not sufficient to control the thyrotoxicosis constantly except in a few mild cases It has also been shown that thiouracil will control the basal metabolic rate prior to operation in the dosage of 300 mg of propyl thiouracil daily and divided into three doses given eight hours apart this is continued until there has been much improvement in the patient s condition at which time it is wise to give 5 to 10 drops of saturated solution of potassium iodide daily for ten days along with the thiouracil ending with the surgical operation Thi

ouracil and related preparations have in some cases been used successfully in controlling thyrotoxicosis without operation, however toxic effects especially on the blood limit its use

Shortly after operation when the occasional stormy reaction has subsided it is usually discovered that the heart condition is much improved if not and the thyrotoxicosis continues further treatment may be necessary With careful preparation and the expert anesthesia and surgery that are essential for the best results remarkable benefits have been frequently secured even in cases which were apparently hopeless because of heart failure and which have been considered generally as poor operative risks The relief of the thyrotoxicosis in such cases has proved far more important in the relief of the heart trouble than have remedies like digitalis and rest in bed directed to aid the heart condition alone It is to be noted further that iodine has far more effect than digitalis in reducing the pulse rate in the tachycardia of thyrotoxicosis per se in fact digitalis is almost invariably ineffective in this respect while iodine is nearly always at first effective

An ingenious therapeutic technic recently introduced for thyrotoxicosis consists of the use of irradiated iodine (I-131) orally adequate control of the disease has been effected without surgery a desirable achievement in cases where the cardiac status is precarious Incidentally as will be noted in the chapters on Coronary Heart Disease (Chapter 21) and on Congestive Heart Failure (Chapter 30) irradiated iodine (I 131) has been used effectively by Blumgart et al (1948) to control both coronary and myocardial insufficiency through the production of a medical thyroidectomy

The therapy of the heart failure due to thyrotoxicosis consists primarily as noted above in the control of the thyrotoxicosis itself by the administration of iodine and operation rest digitalis and diuretics are additional therapeutic measures not very effective however, until the high metabolic rate has been reduced The tolerance of thyrotoxic patients for digitalis is usually quite marked and the therapeutic dose of this drug must be proportionately increased sometimes as much as 50 to 100 per cent above the ordinary dosage in order to obtain any appreciable effect whether beneficial or toxic but only under careful observation

The third therapeutic measure consists of treatment of the atrial fibrillation that may complicate thyrotoxicosis There is little likelihood of control of this arrhythmia while thyrotoxicosis persists but there is a fair chance almost an even chance that relief of the thyrotoxicosis alone will relieve also the atrial fibrillation If it does not do so quinidine will restore normal rhythm in about half of the remaining postoperative cases in whom this arrhythmia persists, while digitalis can be used permanently to control the ventricular rate in the rest of the cases with persistent atrial fibrillation The method of administering digitalis and quinidine will be discussed in Chapters 30 and 33 of this book For paroxysms of atrial fibrillation either before or after thyroidectomy rations of quinidine sulfate (3 to 6 gr 0 18 to 0 36 gm three or four times daily) may be tried they are more likely to be successful after operation

Differential diagnosis Thyrotoxicosis as a cause of cardiac enlargement failure and atrial fibrillation must be differentiated particularly from rheumatic heart disease and essential hypertension Moreover when patients presenting obvious signs of rheumatic or hypertensive heart disease with congestive failure do not obtain relief from the usual therapeutic methods thyrotoxicosis should be suspected as a possible complication

The early stage of thyrotoxicosis before definite cardiac signs have developed is especially to be distinguished from neurocirculatory asthenia Its differentiation is not always a simple matter it is sometimes impossible when the basal metabolic rate is at the normal borderline and there is no definite exophthalmos or thyroid gland enlargement—most of such cases prove later not to have any definite thyrotoxicosis The differential diagnosis requires especial care if one has to deal with a patient who has both neurocirculatory asthenia and a colloid goiter

Rare atypical cases with overactive thyroid glands are found without exophthalmos or goiter a slight staring anxious expression unexplained loss of weight diarrhea pigmentation of the skin and tachycardia may afford clues When in doubt the basal metabolic rate should always be determined and repeated as often as necessary and especially the protein bound iodine in the blood should be determined (normal = 4 0 to 8 0 gamma per cent) or the radioactive iodine uptake (normal = 20 to 50 per cent at the end of 48 hours) Finally a therapeutic test with iodine may be carried out (Means 1937)

HYPOTHYROIDISM MYXEDEMA HEART

The state of underactivity of the thyroid gland consisting typically of myxedema in adults and of cretinism in children is an infrequent condition itself and a still rarer cause of appreciable heart disease However in almost every case some abnormality of cardiac function is evident in the sluggish heart action and especially in the uniform flattening or inversion of all the *T* waves of the electrocardiogram (Figure 92A page 454) these abnormalities are corrected by thyroid therapy (Figure 92B) Enlargement of the x ray heart shadow sometimes at least due to pericardial effusion is also a usual finding in severe myxedema in some cases it is very striking while in others due to the wide range of the normal heart size it may become evident only in the process of taking serial roentgenograms It generally subsides under thyroid treatment with astonishing speed and degree (Figure 93 page 455) Arteriosclerosis likewise is frequent in myxedema

The term myxedema heart has been applied to a condition found in about three quarters of the cases of myxedema (Zondek 1918 1919 Fahr 1925 1927 1932 Fournier 1942) and this will be described below In many cases of myxedema however especially the milder ones it is difficult or impossible to make out any important abnormality of the heart caused directly by this glandular deficiency The cretin too has no very definite heart disease but

shows as in myxedema, abnormal electrocardiographic T waves and sluggish cardiac action

Etiology *Cause* It is evidently the lack of sufficient thyroid secretion in myxedema which occasionally causes definite heart trouble in the form of enlargement or weakness or pericardial effusion for the administration of rations of thyroid gland corrects this trouble In what way the hypothyroidism causes this cardiac abnormality, and what other factors may favor this effect we do not know

Myxedema itself is usually of unknown origin but infrequently it follows thyroidectomy which is carried out to cure thyrotoxicosis Myxedema was intentionally produced about 18 years ago in a new treatment of intractable angina pectoris and myocardial insufficiency by the surgical operation of total thyroidectomy (see Chapters 21 and 30) but this form of treatment was

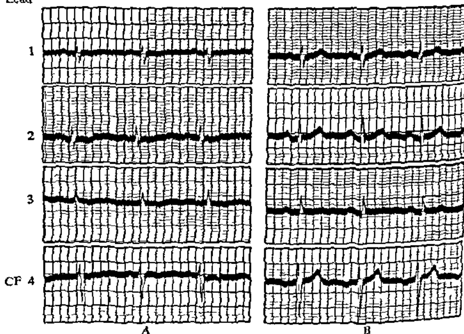


FIG 92 Electrocardiograms (four leads) in hypothyroidism (myxedema) male age 59 (*A*) before and (*B*) after thyroid therapy Basal metabolic rate at time of (*A*) = —46 per cent and at time of (*B*) = —17 per cent

found impracticable and given up However there has been recently a revival of the principle of therapy involved in the form of a medical thyroidectomy via irradiated iodine with prevention of any high degree of hypothyroidism by the administration of small doses of thyroid

Age The myxedema heart like myxedema itself has been found usually in middle age or later but it may occur in youth It is likely that a complication such as coronary heart disease coming independently or favored by the myxedema may help to account for the greater frequency of cardiac dilatation and weakness among the older victims of myxedema

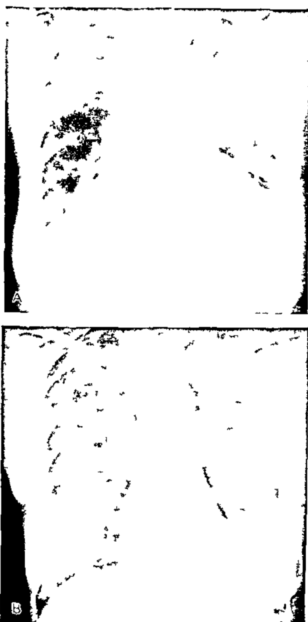


FIG 93 Roentgenograms showing great change in cardiac area (6 cm in the trans ve se diameter of the heart shadow) as the result of the successful treatment of myxedema by thyroid administration Woman 66 years old

(*A*) Dec 5 1934 basal metabolic rate = —46 per cent

Cardiothoracic ratio in roentgenogram $= \frac{18\ 2}{24\ 0}$

(*B*) May 21 1935 basal metabolic rate = —13½ per cent

In this record the diaphragm is somewhat lower than in the former which exaggerates slightly the difference in size of the heart shadow

Cardiothoracic ratio $\frac{12\ 2}{23\ }$

(Kindness of Dr J C Gant Madison College Tennessee)

Sex Sex has no particular relationship to the myxedema heart so far as we know

Other factors The most important factors controlling the incidence of the myxedema heart in any community are undoubtedly first the frequency of myxedema itself in that community, and second the ability of the medical profession to recognize and properly to treat it It undoubtedly is a preventable type of heart disease

Pathology An occasional finding in myxedema is considerable globular enlargement of the x ray heart shadow giving rise to the so-called myxedema heart The exact cause of such enlargement is not always clear and has been a subject of some controversy probably it is the result partly of dilatation partly perhaps of the increased bulk due to the myxedematous state affecting the heart tissues and certainly sometimes to an excess of fluid in the pericardium all three factors may play a role in increasing the area of percussion dullness or the roentgen ray heart shadow Functional regurgitation through the atrioventricular valves may occur with the dilatation but there is no endocarditis Pericarditis is not found despite the occasional discovery of large pericardial effusions the heart itself may show no actual enlargement in the midst of a large pericardial effusion Presenile arteriosclerosis especially involving the coronaries is reputed to be a general accompaniment of myxedema but convincing evidence of this is still lacking

Symptoms There are few symptoms of the heart involvement in myxedema the low level of activity in this condition probably preventing the cardiac dilatation and weakness from making themselves more evident Dyspnea has been noted in rare cases of congestive failure in myxedema and in a few patients with myxedema angina pectoris has occurred These symptoms occurring at the height of the endocrinopathy itself are sometimes cleared by thyroid therapy but sometimes induced or aggravated by the specific treatment which raises the metabolism and blood flow too rapidly coronary disease or other factors preventing the heart itself from keeping pace with the demands thus newly thrown upon it

Signs The only cardiovascular signs in the case of the myxedema heart are the occasional enlargement evident both on physical examination and by roentgen ray study (Figure 94) the sluggish heart action commonly observed in the same way and the constant finding of absence or inversion of the *T* wave in all leads of the electrocardiogram (Figure 93) This electrocardiographic sign is almost pathognomonic of myxedema and can be used along with the determination of the basal metabolic rate in following the progress of thyroid therapy There is frequently also a decrease in amplitude (low voltage) of the other complexes of the electrocardiogram the *P* and *QRS* waves which resume along with the *T* waves a more normal extent of excursion on treatment

The usual signs and symptoms of myxedema are generally obvious—slowed mental state dryness and thickening of hair and skin puffiness of subcutaneous tissue (myxedema) all over the body including the face weakness and dislike of cold The basal metabolic rate is generally reduced to 30 per cent below

the average normal or lower borderline cases with measurements of basal metabolic rate of minus 10 to minus 25 per cent are less likely to have heart trouble and usually these individuals have not true myxedema to start with

Also in myxedema a decrease has been found in the cardiac output circulatory velocity, peripheral flow, and total volume of blood

Course and prognosis The finding of evidence of significant cardiac involvement in myxedema is an important sign for it means that the grade of myxedema is a serious one or that other heart trouble such as coronary or hypertensive is present The discovery of cardiac enlargement is usually an incidental one in the course of routine examination but it should always be looked for and the cardiac response to the treatment of myxedema should be carefully followed Sudden death with or without angina pectoris may occur a few months or years after the finding of the myxedema heart Death postponed by careful thyroid therapy may come eventually from other complications without cardiac responsibility in fact a full length of life is possible under careful treatment Congestive failure as a cause of death in myxedema per se is very rare I myself have never seen a case

Complications Angina pectoris due to coronary disease is the most important complication of the myxedema heart especially after treatment of the myxedema has begun the elevation of metabolism by thyroid therapy may induce symptoms of coronary insufficiency Acute infections like pneumonia may appear as complications with serious prognosis General arteriosclerosis is common but not essential

Treatment. Digitalis has no definite beneficial influence on the cardiac enlargement or electrocardiographic abnormalities of myxedema Thyroid gland on the other hand has a striking effect clearing up these conditions more or less completely if given in sufficient dosage An amazing decrease in heart or pericardial size may sometimes be effected in four cases of Lerman Clark and Means series (1933) for example the transverse diameter of the heart shadow by teleroentgenogram decreased in the first case from 19 3 to 12 4 cm in six months in the second from 21 4 to 15 7 cm in six weeks in the third from 16 5 to 11 4 cm in eight and one half months and in the fourth from 19 4 to 15 5 cm in five months

Thyroid gland should be given very cautiously in the treatment of myxedema particularly when there is a history of angina pectoris for although marked general improvement may ensue and the heart resume practically normal size angina pectoris may be precipitated or increased by the raised level of metabolic rate and increased blood flow and sudden death may occur just when the myxedema itself is under control It may be necessary to give doses of thyroid so small that although the basal metabolic rate is not restored completely to normal angina pectoris is kept away or under partial control some myxedematous signs and symptoms may remain but life is prolonged A dose of ¼ to ½ gr (0 015 to 0 03 gm) of thyroid (U S P) daily may accomplish this instead of the usual larger doses (1 to 2 gr) Rarely the thyroid therapy banishes angina pectoris Digitalis should be given if there are in addition to the dilatation of the heart signs and symptoms of congestive failure

which do not yield to thyroid therapy alone but morphine is contraindicated

Differential diagnosis The myxedema heart must be differentiated from cardiac enlargement and weakness of other cause, from coronary heart disease and from infectious pericardial effusion This is usually readily done by the absence of cardiac symptoms of chronic valvular disease, and of hypertension by the typical electrocardiographic findings by the general signs of myxedema and by the response to thyroid therapy

DISEASES OF OTHER GLANDS

Parathyroid disease Little is to be said of the effect of parathyroid disease on the heart The decreased calcium content of the blood in tetany is associated with increase of the duration of cardiac systole, hyperparathyroidism and the administration of excessive amounts of parathormone cause by the increase of calcium content of blood an increase of calcium in the tissues likewise including the heart muscle We have no proof that these results are of any clinical significance

Pituitary disease The only association of abnormality of the heart with pituitary disease is the finding of cardiac enlargement (hypertrophy) especially of the left ventricle in acromegaly such enlargement may be great and out of proportion to the general splanchnomegaly found in this condition Whether it is the result of the somewhat increased basal metabolic rate in this disease or due to other factors is not known In one series of 24 patients marked heart failure was noted in 18 (75 per cent) six of this group died from that cause (Mason, 1936 1938) In gigantism the heart is not affected but bears a normal relationship to body size (Zondek 1920)

Basophilia of the posterior lobe of the pituitary gland has been noted in certain cases of pituitary adenoma with hypertension and in some patients with hyperpiesia and eclampsia (Cushing 1934) this finding has not been confirmed however as a characteristic occurrence in essential hypertension

Adrenal disease Adrenal disease has a direct effect on the heart as well as on the circulation Destruction of adrenal tissue (cortex) as in Addison's disease causes collapse marked hypotension and general muscular weakness including myocardial weakness but not structural heart disease The heart is smaller than normal both in volume and weight in part the result of the decreased amount of circulating blood and in part due to myocardial atrophy and the *T* waves of the electrocardiogram are depressed

Relief of the symptoms and signs of Addison's disease has been effected by adrenal plus sodium chloride therapy but the new specific therapy of adrenal insufficiency (Addison's disease) with desoxycorticosterone and cortisone must be followed with great care since serious cardiac enlargement and weakness may appear with toxic doses in fact measurement of heart size has been suggested as an objective check on large dosage of the hormone (McGavack 1942) it has been found that the dose of desoxycorticosterone acetate necessary to produce a given degree of cardiac enlargement varies inversely as the amount of sodium available in the tissues

Not only may dilatation of the heart result from excessive desoxycorticos terone therapy of Addison s disease but even high degrees of congestive failure along with changes in the electrocardiogram which recede or disappear when the drug is omitted The tendency to low voltage of the *QRS* and *T* waves found with Addison s disease is much exaggerated by excess of desoxycorticosterone (Currens and White 1944) These changes in the heart are probably due to or at least associated with a loss of body potassium Illustrations of the changes in the electrocardiogram and roentgen picture of the heart due to excessive desoxycorticosterone therapy are shown in Figure 94 on page 460

The stimulation that results from an adrenal medullary tumor (*pheochromocytoma*) can cause hypertension of paroxysmal nature which may be cured by removal of the tumor If the hypertension is sustained however removal of the tumor may have no effect on it splanchnic resection then being required The tumor may be located in tissue outside the adrenal glands themselves and then may be found with difficulty

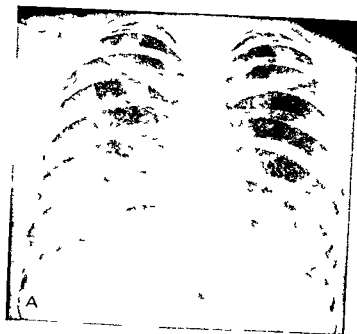
Cortical adenomas of the adrenal may also play a role in hypertension they are more numerous than pheochromocytomas but their removal may not have any important effect on the hypertension present in such a case (Smithwick personal communication 1942)

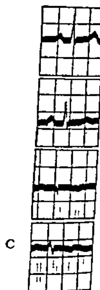
Pancreatic disease *Diabetes mellitus* does not cause heart disease directly but it does favor arteriosclerosis and coronary artery disease (Root Bland Gordon and White 1939) At least 50 per cent of all diabetics die as a result of cardiovascular complications and the relative incidence of this cause of death is steadily increasing as other fatal complications are eliminated Marked atherosclerosis of the aorta with considerable dilatation is common Hypertension plays an important role in this group and frequently precedes the onset of the diabetes sometimes by several years Congestive failure due to hypertension or to coronary disease is not unusual but death comes most frequently from coronary occlusion (West 1935)

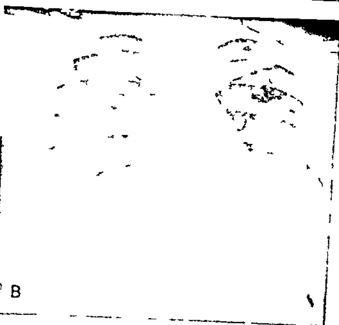
Excess of insulin does not apparently affect the heart seriously unless there is already heart disease the possible harmful effect from insulin shock (*hyper insulinemia*) however makes it advisable to use insulin cautiously in the presence of acute coronary thrombosis very severe angina pectoris and congestive failure Arrhythmias and electrocardiographic abnormalities following the use of insulin occur

Thymic disease Hypertrophy or persistence of the thymus gland is not attended by heart disease but is accompanied by general arterial hypoplasia The cause of the sudden death in the so-called status lymphaticus and its reputed relationship to the thymus gland are still unsolved mysteries The enlarged gland in child or adult is to be differentiated on physical examination and by roentgen ray from abnormalities of the great vessels

Genital glands Heart disease does not result from disease of ovaries or testes but functional disorders with cardiovascular symptoms of neurocirculatory asthenic type are commonly found especially at the time of the menopause in women or following double oophorectomy Hypertension of the essential type is also a frequent finding often but temporary at the time of







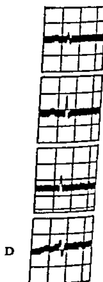


FIG 94 Roentgenograms and electrocardiograms in the case of a young woman with Addison's disease showing the toxic effect of excessive desoxycorticosterone acetate in treatment (*A*) Roentgenogram of the thorax Aug 13 1942 showing normal heart size and some prominence of the shadow of the pulmonary artery (*B*) Roentgenogram of the thorax Sept 9 1942 showing marked enlargement of the heart during the height of the effects from the desoxycorticosterone (*C*) Electrocardiogram more or less normal of this patient on Oct 24 1942 after the effects of the desoxycorticosterone had worn off (*D*) Electrocardiogram on Aug 30 1942 at the height of the toxic effect of the desoxycorticosterone

the menopause and this may affect the heart secondarily to cause hypertrophy Hamilton (1940) has not found however that the climacteric exerts any very severe strain on the heart of women already affected by heart disease A so-called fibroid heart has been said to result from uterine fibroid disease (fibroma) but there is no proof that such a condition exists, functional dis turbances as noted above and premature beats undoubtedly accounting for this condition There has as yet been demonstrated no real myoma heart" (von Jaschke 1933) A change in the electrocardiogram consisting of a digitalis like depression of the *ST* segments and *T* waves, was noted by Scherf (1940) in some females with ovarian dysfunction and was cleared by estro genic hormone therapy such changes are however rarely more than slight in degree and it is probable that some factor such as hyperventilation (see Chapter 9) secondary to the climacteric rather than the ovarian dysfunction itself is responsible

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CHAPTER 19

HYPERTENSIVE HEART DISEASE ESSENTIAL HYPERTENSION HYPOTENSION

HYPERTENSIVE HEART DISEASE

Introduction Since the last revision of this book seven years ago there have been innumerable studies and published reports concerning hypertension and hypertensive cardiovascular disease many of them of considerable interest and value, as may be observed on perusal of the additions of references to representative publications in the Bibliography at the end of the chapter Nevertheless the mechanism of the so-called essential type of hypertension still eludes us *another few years may very well reveal to us the answer*, or the answers since so many able workers are engaged on the problem Meanwhile to date distinct advances in therapy, though empirical have been scored

The most common and important of all types of heart disease by and large the world over is that due to systemic hypertension with elevation of the *diastolic* blood pressure It is often serious and frequently followed by congestive failure and death It has been estimated that nearly 100 000 people die annually in the United States (population of about 130 000 000) as the result of heart failure due to hypertension and that 7 000 more die from other consequences of high blood pressure In a series of 30 265 autopsies with 4 678 cardiovascular deaths (15 45 per cent) 2 597 were hypertensive cases (55 5 per cent of the cardiovascular deaths and 8 6 per cent of the total autopsies) the chief factor responsible for the hypertensive deaths was cardiac (2 059 cases or 79 per cent divided into the group with myocardial insufficiency—congestive heart failure—with 1 124 cases or 43 per cent and that with coronary fatalities with 935 cases or 36 per cent) while cerebral hemorrhage caused death in 362 patients (14 per cent) and renal insufficiency in 176 cases (7 per cent) (Clawson 1941) In New England systemic hypertension is a primary or a secondary factor in at least 30 per cent of cases of heart disease Until the last decade or two the condition had a variety of other names or was missed entirely unless blood pressure studies revealed the hypertension It has made up a considerable percentage of cases of so-called cardiorenal disease , of so-called myocarditis and of cardiac enlargement or failure without valvular disease and of unknown cause

Heart disease due to pulmonary hypertension is much less common than that due to systemic hypertension but it is of considerable interest and importance and will be discussed in the next chapter Hypertension in the portal circulation will be taken up in connection with diseases of the blood vessels in Chapter 28 Venous hypertension is discussed in Chapter 6 under Venous Blood Pressure and in Chapter 30 on Congestive Heart Failure

Etiology *Cause* The cause of the heart disease is known—high blood pressure often abetted by some other factor especially coronary disease The fundamental cause of the high blood pressure in the majority of cases has been however obscure and not associated with any constant clinical findings hence it has been called essential or primary The term hyperpiesia (ὑπέρ over and πιέζειν to press) has also been applied to it and another synonym is vascular or arterial hypertension indicating that the blood vessels are responsible

Innumerable theories as to the cause of hypertension have been advanced since its discovery over a generation ago and some of these theories have now become facts in other words there are at least several different causes although that of the bulk of the cases (those with essential hypertension) is still (1951) to be elucidated The association of heart disease with kidney disease was demonstrated by Bright more than a century ago (1836) but the mechanism of such association was of course unknown Gull and Sutton (1872) pointed out the arteriolar fibrosis found in Bright s disease and in our own generation the vascular factor in hypertension has had the limelight During the last decades however attention has been directed again to the kidneys by the pioneer work of Goldblatt (1934) who demonstrated that hypertension can be produced in animals by obstructing by a clamp the blood flow through a renal artery and by the finding of pressor substances called angiotonin and hypertensin produced by the kidney with their neutralization by other (antipressor) substances (Tigerstedt and Bergmann 1898 Houssay Fasciolo and Taquini 1938 Page and his associates 1940 1941 Harrison Grollman and Williams 1940) Suffice it to say that the most acceptable and widely held theory in the light of our present knowledge is that the arterioles more or less universally throughout the body have through some direct toxic or nervous influence become irritable and pass into a state of vasoconstriction thereby increasing the resistance to the circulation of blood to which the heart responds with a resulting rise of arterial blood pressure It is possible that the renal arterioles may play the major role in this process At first this type of hypertension is slight and transient and may largely escape notice Its later course is very variable the *arteriolar spasm* may subside with a spontaneous cure of the hypertension it may increase and become fixed as in the ordinary well recognized case or it may progress to an extreme and rapid degree giving rise to the so-called malignant hypertension According to this theory there are at first no (as yet) recognizable pathologic changes arteriolar sclerosis arterial sclerosis renal damage (arteriosclerotic nephritis) and cardiac enlargement are secondary effects of long sustained hyperpiesia in-

time the *arteriolar sclerosis itself* may be responsible for at least some of the hypertension and prevent its reduction

Hypertension is in some cases (a distinct minority) secondary to an easily discoverable cause such as gross nephritis polycystic kidneys adrenal tumor increased intracranial pressure, or congenital coarctation of the aorta or is temporarily induced by urinary obstruction congestive heart failure coronary insufficiency, pain exertion or excitement or concussion of the brain, frequently slight systolic hypertension attends thyrotoxicosis complete heart block and aortic regurgitation or marked sclerosis Under such circumstances the hypertension is not called essential or hyperpiesia In the case of hypertension of renal origin there may be an added toxic effect from renal insufficiency with or without definite uremia The surgical kidney as such is not however commonly a cause of hypertension

A number of practical classifications of hypertension have been proposed in the past a good example of which presented by Gilchrist (1941) was published in the third edition of this book A recent system, bringing this subject up to date has been presented by Page (1949) This is reproduced below It is to be observed that diastolic hypertension is far more important than systolic hypertension systolic hypertension with normal or only very slightly elevated diastolic blood pressure is much less important clinically and is apparently in the main the result of arteriosclerosis

Table 8

CLASSIFICATION OF HYPERTENSION (PAGE)

Clinical	*Experimental*
I Nervous Participation	
Poliomyelitis of brain stem	Cerebral ischemia
Porphyria	Cushing s experiment
Increased intracranial pressure	Resection of sinus and aortic depressor nerves
Sclerosis of carotid sinus	
Resection of glossopharyngeal nerve	Hypertension from audiogenic stimulus
Emotion	
Tabes dorsalis	
II Cardiovascular Participation	
Coarctation of aorta	Clamping of aorta above renal vessels
Heart failure	
Arteriovenous fistula	
Arteriosclerosis	
III Endocrine Participation	
Hypophysis—basophil adenoma	Anterior lobectomy diminishing blood pressure
Adrenals—pheochromocytoma	
Cortical carcinoma	Adrenaline hypertension
Cortical hyperplasia	Desoxycorticosterone acetate hypertension
Thymus—*carcinoma with Cushing s syndrome*	Bilateral adrenalectomy abolishes hypertension
Placenta—associated with toxemia of pregnancy	Cerebrum (1951)

IV Renal Participation

Glomerulonephritis
Obstruction to renal vessels
Pyelonephritis
Prostatic obstruction
Polycystic kidneys
Crush syndrome
Periarteritis nodosa
Perinephric constriction of the paren chyma
Antikidney serum nephritis
Mechanical constriction of renal ar teries or veins
Mechanical compression of ureters
Cellophane or silk perinephritis

Hyperpiesia (essential hypertension) accounts for fully 95 per cent of the cases of hypertensive heart disease and obvious renal disease for most of the rest About two thirds of the cases of established diastolic hypertension show cardiac enlargement on examination Still others have lesser grades of enlarge ment too slight to discover clinically hypertension whether or not of the essential type may be too slight or recent in onset to cause any cardiac hypertrophy at all

Age Hypertensive heart disease like hypertension itself (especially hyper piesia) is commonest in middle age and after signs of it appear on the average ten years after the onset of sustained hypertension of an important degree except when there are complications (valvular disease or coronary disease) to make its effect more quickly evident Of a series of 708 cases of hypertensive heart disease 62 per cent were in the sixth and seventh decades (29 per cent in the sixth and 33 per cent in the seventh) 17 per cent were over seventy years of age 16 per cent were in the fifth decade 4 per cent in the fourth 1 per cent in the third and 0 5 per cent were below twenty years old thus only 21 per cent of the cases were less than fifty years of age (White and Jones 1928) In a more recent series of 1 249 cases 68 per cent were between fifty and seventy (White 1936) The youngest case of essential hypertension with autopsy on record that I know about has been reported by Taussig and Remsen (1935) a colored boy two years old

Sex There is not much difference between the sexes in the incidence of hypertensive heart disease In White and Jones series of 708 cases 55 per cent were female and 45 per cent male In the more recent series of 1 249 cases from my own practice 51 per cent were male and 49 per cent female Hypertension itself on the other hand is far more common in females than in males by a ratio of about 2 to 1 Yet it is true that it is much more serious in the male Blackford and Wilkinson (1932) found the mortality rate after ten years twice greater in men and among 50 consecutive cases of my own with serious cardiovascular sequelae of hypertension selected for sympathec-tomy 38 were male and 12 were female (White et al 1950)

Heredity Of all known etiologic factors in the production of hypertension and so of hypertensive heart disease heredity ranks as of the greatest im portance Frequently many members of one family in the course of a few

generations have either shown essential hypertension or have had troubles coming from such a condition The way in which heredity acts is obscure but we do know of its great significance

Race and *climate* are factors of some importance Hypertension is less marked in tropical and semitropical climates and it is said to be uncommon in certain nationalities like the Chinese when in their own country whether this is because of race or of other factors like tempo of life or diet we do not know It is especially common among the Negroes in the United States apparently twice as common as in the white population for reasons unknown it is said that in Africa on the other hand hypertension is rare among the Negroes who tend however to succumb to other ills especially tropical diseases at relatively early ages before the years when essential hypertension is at its peak in America We need much international research on this problem

Diet and obesity Overeating and obesity frequently are associated with hypertension and hypertensive heart disease but the relationship is a very inconstant one on both sides A high protein diet was once blamed for the production of hypertension but this has been refuted, on the other hand a diet overrich in food value in general may be of importance During the war in Holland over a period of starvation from September 1944 to May 1945 there was a frequent lowering of blood pressure associated with weight loss especially in hypertensive patients (Lups and Francke 1947) There are problems here in need of solution

Nervous and physical strain It is believed by many observers that a life of high nervous tension favors the production of hyperpiesia or at least its aggravation the latter is the more likely Physical strain and constant laborious work although sometimes blamed as aggravating factors have been largely exonerated in late years indeed it seems possible that physical exercise in moderation at least may protect against hyperpiesia

Endocrine disturbances are frequently attended by hypertension but rarely by marked hypertension these disturbances are especially associated with the ovarian function (for example, menopause and oophorectomy), with thyrotoxicosis and with adrenal or pituitary tumors In the case of thyroid or adrenal or pituitary oversecretion surgical removal of a large part of the thyroid gland or of an adrenal or pituitary tumor may result in a return of blood pressure to normal The discovery that an excess of basophilic cells is present in the posterior lobe of the pituitary gland (hypophysis) in certain cases of pituitary adenoma with hypertension and of eclampsia (Cushing 1932) suggested that hyperpiesia might have its basis therein but this suggestion has not been confirmed only a small minority of cases are to be so explained

Infections and poisons have not been shown to have any close connection with the pathogenesis of hyperpiesia this statement includes lead long blamed for hypertension

Pathology The pathology of hypertensive heart disease is as a rule very

simple Both cardiac and vascular abnormalities in chronic hypertension are primarily but natural responses of muscle to increased work Hypertrophy of the individual muscle fibers of the left ventricle is always present sometimes to such a degree that the heart is greatly enlarged (Figure 95) A heart weight of about 500 gm (normal = 200 to 350 gm) is common and in rare cases this may be increased to 750 or even to 1 000 gm With the development of failure

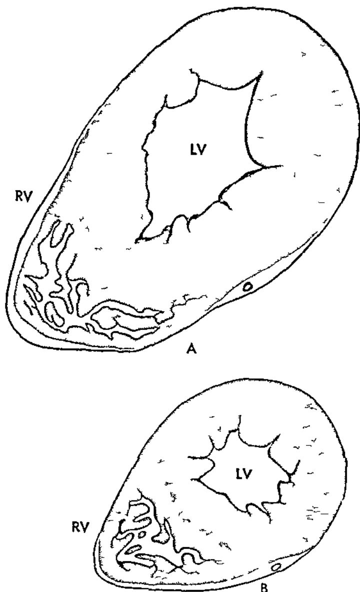


FIG 95 Drawings showing cross sections (actual size) of (*A*) an enlarged hypertensive heart and of (*B*) a normal heart at a level two thirds of the distance from base to apex of the ventricles LV = left ventricle RV = right ventricle

dilatation appears changing the appearance of left ventricular hypertrophy from concentric to eccentric Such left ventricular dilatation is followed by dilatation of the mitral valve ring functional mitral regurgitation dilatation of the left atrium and enlargement of the right ventricle and atrium too if the left ventricular failure lasts long enough It has been suggested that the primary hypertrophy of the heart muscle begins only after it has been strained *or traumatized and somewhat dilated by the early efforts to overcome the* effect of the arteriolar constriction Since with systemic hypertension the pulmonary arterial blood pressure usually remains normal (until the left ventricle fails) the right ventricle is unaffected early in the disease Eventually after the left ventricle has begun to fail the pulmonary blood pressure rises and the right ventricle in its turn is subjected to considerable strain and begins to enlarge as a matter of fact the commonest cause of right ventricular enlargement is failure of the left ventricle secondary to systemic hypertension

There is no actual myocarditis or myocardial degeneration in most cases of uncomplicated hypertensive heart disease even in massive hearts with marked congestive failure, some myocardial scarring (fibrosis usually in small areas) is however not uncommon even in the absence of coronary disease (Levine V 1934) Endocarditis and pericarditis do not occur primarily in this type of heart disease although endocardial sclerosis most marked in the left atrium which first bears the brunt of left ventricular failure was found in all of a series of 27 hypertensive hearts (Levine V 1934)

The aorta normal at first becomes dilated in older and chronic cases but never to the degree observed in advanced syphilitic aortitis Some of the dilatation seen by roentgen ray examination is not found post mortem since it is temporary depending on the intra aortic hydrodynamic state The vascular dilatation may extend a little into the aortic branches especially into the innominate *and carotid arteries Rarely the aortic media may split* to cause a dissecting aneurysm when hypertension is complicated by an abnormally weak spot in the aortic wall

Thickening of the arteries and arterioles throughout the body is a common finding in chronic hypertension and in all probability is a vascular response to the hypertension Arteriolar sclerosis and obliteration may complicate the picture Hypertension without arteriosclerosis and arteriosclerosis without hypertension are frequent findings but the two combined are as frequent as either condition alone Renal arteriolar sclerosis is preponderant and is universally found in the higher grades of hypertension although not as a rule at the onset of the disease

Symptoms There are no symptoms of hypertensive heart disease until complications arise the condition is often discovered incidentally in the course of routine examination Usually the person feels perfectly well and is simply annoyed by the discovery of the high blood pressure or of the enlargement of the heart Occasionally however, there are headaches and a coincident neurocirculatory asthenia with its various symptoms including palpitation heartache and dyspnea These symptoms are frequently erroneously attributed

by patient and doctor alike either to the high blood pressure or to heart dis ease although it is true that a person subject to neurocirculatory asthenia will have more symptoms if the blood pressure is high and the heart is enlarged than when the blood pressure and heart are normal and in some cases head ache is part of a disturbance of the cerebral circulation incident to the hypertension (hypertensive encephalopathy) A neurosis is common with hypertension and hypertensive heart disease usually the result of fear of the high blood pressure When true symptoms of hypertensive heart disease do arise they are most commonly those of cardiac insufficiency which may in crease to well marked congestive failure resulting from the myocardial strain and fatigue which involve primarily the left ventricle

Dyspnea on exertion is usually the first authentic symptom tending to in crease in degree unless checked by the institution of proper treatment With marked failure dyspnea may become constant and prevent a recumbent posi tion (orthopnea) Or there may be sudden attacks of acute failure of the left ventricle occurring during sleep at night or less often in the daytime after exertion or excitement with engorgement of the pulmonary circulation pul monary edema and sometimes the setting off of asthmatic respiration Such an attack of wheezing is called cardiac asthma and is not an infrequent syn drome in the case of the failing hypertensive heart it varies considerably in duration but lasts usually about an hour

Pain is less common in hypertensive heart disease than is dyspnea It takes two forms sometimes a precordial ache due to an associated neurocirculatory asthenia (or effort syndrome) aggravated by the cardiac enlargement and sometimes angina pectoris from an associated coronary disease or syphilitic aortitis Angina pectoris however though common in hypertension because of the age incidence is not so characteristic as is dyspnea for the hypertensive strain results in an inability of the left ventricle to maintain the general cir culation more often than in the inability of the coronary circulation to supply the heart muscle with blood unless we accept the possible theory that some hypertension especially if it involves the diastolic pressure may result from the need of greater force to maintain an adequate coronary circulation The prolonged pain of coronary occlusion occasionally complicates hypertensive heart disease

Palpitation is common in hypertension with or without heart disease espe cially in sensitive persons due either to the consciousness of the forceful heart action with normal rhythm particularly on exertion or excitement or to the occurrence of unimportant premature beats paroxysms of tachycardia or atrial fibrillation These various disturbances of rhythm are common in hypertensive heart disease but they are not characteristic Of the group of 708 cases of hypertensive heart disease of White and Jones (1928) 92 (or 13 per cent) had atrial fibrillation (14 of these were paroxysmal in type) paroxysmal tachycardia was noted in 11 patients (1 5 per cent) atrial flutter in 2 (0 3 per cent) and atrioventricular block in 13 (1 8 per cent)—the last named being due to an associated coronary disease and not to the hypertension

Other symptoms frequently found in essential or in nephritic hypertension with or without heart disease are familiar tinnitus weakness nosebleeds or other hemorrhages symptoms of cerebral accident (aphasia and paralysis) whether transient (hypertensive cerebral vascular crises or minute lesions) or more or less lasting (cerebral hemorrhage or thrombosis), and symptoms of renal insufficiency (drowsiness coma and vomiting from uremia) The term hypertensive encephalopathy is used to cover all the various cerebral vascular disturbances due to hypertension from slight dizziness to extensive apoplexy, in frequency as a serious complication it ranks below the cardiac effects but above the renal

Signs The only constant sign of hypertensive heart disease is cardiac enlargement due mainly to left ventricular hypertrophy The hypertension itself responsible for this enlargement may have subsided at the time of examination though some trace of it usually exists If there is no increase in heart size even though hypertension is present we cannot label the condition hypertensive heart disease although as after rheumatic fever we may speak of potential heart disease In the early stages of hyperpiesia and even in more chronic cases when the blood pressure is but slightly elevated the heart may be able to stand the strain without increase in size but a normal heart size is rare if it exists at all, with markedly high blood pressure of long duration Finally it is to be observed that the cardiac enlargement of hypertensive heart disease may be present in slight degree to be discovered only at postmortem examination not being sufficient to give evidence during life An addition to the heart weight of 25 50 or perhaps even 100 gm in the absence of dilatation can probably not be detected clinically even by careful roentgen ray examination unless there are frequent serial records Hence the clinical statistical report that about two thirds of the cases with hypertension eventually show cardiac enlargement undoubtedly falls somewhat short of the actual figure as indicated by the statistical study of Murphy and his associates (1932) who found that in a series of 375 cases of essential (primary) hypertension examined postmortem the heart weights were 400 gm or above in 81 87 per cent (normal upper limit of heart weight = 350 gm in the male and 300 gm in the female)

In systemic hypertension with or without heart disease the aortic second heart sound is usually accentuated sometimes to a striking degree When the left ventricle begins to fail the pulmonary second heart sound increases in intensity in its turn as the pulmonary blood pressure rises and finally the pulmonary second sound equals or quite commonly exceeds the aortic second sound in intensity even though the latter continues to be louder than normal The changing relationships of the intensities of these two sounds is of great interest and importance affording a valuable but much neglected clue to the degree of sufficiency of the left ventricle

With increasing size of heart and the development of dilatation of left ventricle and aorta under the strain of the hypertension apical and aortic systolic murmurs appear and are common in the more advanced cases the former due to functional mitral insufficiency and the latter chiefly to the aortic dilata

tion In still more advanced cases especially when arteriosclerosis complicates the picture the aortic valve ring itself may stretch either temporarily under the head of pressure or more or less permanently to give rise to an aortic diastolic murmur (aortic regurgitation usually functional) In a series of 500 cases of hypertension (Paullin 1927) a mitral systolic murmur was noted in 26 per cent an aortic systolic murmur in 6 per cent and an aortic diastolic murmur in 2½ per cent in another series of 200 consecutive autopsied cases of hypertensive heart disease with normal aortic valves reported by Garvin (1940) a diastolic murmur had been heard at the base of the heart apparently aortic in origin in 14 cases resulting in a frank error in etiologic diagnosis in four instances

The aortic dilatation due to hypertension may not be marked enough to be found on physical examination but it is generally easily seen fluoroscopically It consists of a general enlargement of the whole thoracic aorta The ascending aorta is not as a rule so dilated as in syphilitic aortitis and there are no aneurysmal pouches A point of especial interest concerning the aortic dilatation in hypertension and incidentally also in cases of aortic regurgitation is that the dilatation is at first functional or dynamic at that stage failing to appear at autopsy even though very evident by roentgen ray examination during life

A common sign resulting from two factors the vascular dilatation and the pushing up of the great vessels by the cardiac enlargement and the high diaphragm so often found in obese persons especially women with hypertension is a prominence with pulsation of the innominate artery and the origin of the carotid artery at the base of the right side of the neck just above the inner end of the clavicle this is so marked sometimes that it resembles a small aneurysm

When congestive heart failure arrhythmias or other complications arise the usual signs of such troubles appear and the heart tends in the case of failure to become very large with increasing dilatation The appearance of gallop rhythm of the protodiastolic type is a frequent and serious sign of cardiac dilatation and failure in hypertensive heart disease The relative frequency of arrhythmias in hypertensive heart disease has been noted above their incidence is less in hypertension as a whole One of the most important disorders of heart action—pulsus alternans (see Chapter 8)—is relatively common in the case of the failing hypertensive heart and is much more common than generally thought it is most readily detected during the course of blood pressure measurement and it usually means that death is at best but a few years off (see Chapter 30)

One of the most helpful and constant signs of chronic hypertension and therefore usually associated with hypertensive heart disease is sclerosis of the arteries in the eye grounds (fundi oculorum) this is far more constant than in the case of general or coronary arteriosclerosis or of nephritis In slight to moderate grades of hypertension there may be little change in the fundi from none at all to silver wire appearance of the arterioles with nicking of the veins where the arteries cross them but in advanced or serious cases

hemorrhages appear in the eye grounds and areas of degeneration are found (see Figure 9 page 54) Moreover an early finding of marked retinal changes suggests that the type of hypertension is malignant" with a bad prognosis (even though the kidneys may be relatively normal at the time)

Signs of serious involvement of the brain may appear in the course of hypertensive heart disease such as paralyses and abnormal reflexes or there may develop evidence of involvement of the kidneys albuminuria many casts in the urinary sediment oliguria low specific gravity of urine lowered renal function and nitrogen retention in the blood but it is to be remembered that in congestive heart failure due to hypertension albuminuria casts and other urinary abnormalities may be caused by congestion without nephritis and that a relatively unimportant vascular nephritis may develop secondarily due to the hypertension with such signs as those noted above and without congestive failure

The blood pressure in hypertensive heart disease generally remains high but sometimes either because of spontaneous remission or because of heart failure or general vasomotor collapse and in some cases evidently aided by treatment it may fall to average normal or nearly normal levels leaving obscure the cause of the cardiac enlargement and failure unless knowledge exists of the previous hypertension The diastolic pressure in such cases may be maintained at a somewhat high level (100 to 110 mm for example) even though the systolic pressure has fallen to 150 mm or below this relatively high diastolic pressure and low pulse pressure may in some cases reveal the previous hypertension In fact as already noted in the discussion of the clinical classification of hypertension the systolic level of the blood pressure is far less important than the diastolic so far as strain on heart arteries and kidneys is concerned a rise of a few millimeters of mercury of diastolic pressure is a great deal more serious than several times that rise of systolic pressure A full pulse pressure with elevated systolic pressure and normal diastolic is common in advanced sclerosis of the larger arteries (with loss of elasticity) and relatively normal arteriolar circulation (that is, without essential hypertension)

It is not known how frequently cardiac enlargement is the result of an old hyperpiesia in the absence of hypertension at the time of examination and without evidence of valvular disease serious coronary disease pulmonary fibrosis or pericardial disease Some writers believe that it is always or almost always so produced This is a possibility but by no means a certainty Some causes for enlargement of the heart exist which are not yet clear while others previously unrecognized have in recent years been brought to light More study of this problem is needed

The systolic pressure in established hypertension varies from 150 to over 300 mm of mercury it is usually about 200 The diastolic pressure varies from 90 to 180 but is usually 110 to 120 The pressure readings (especially the systolic) vary greatly among different individuals and on different occasions in the same individual Repeated measurements must often be made before the customary basal blood pressure levels for a given patient are dis

covered uninfluenced by excitement exertion or fatigue It has been found as would be expected that the blood pressure levels recorded by the patient himself or herself at home tend to be distinctly lower than they are in the clinic or doctor s office (Ayman and Goldshine 1941) It must be remembered however that neither record is truly representative and that hypertension until fixed is likely to go through wide swings from day to day or hour to hour The lability of the pressure is of some importance in prognosis and treatment too the more favorable cases tending more often to show pressures close to normal To test the degree of the lability various procedures have been introduced including especially (1) the *measurement* of the blood pressure *at frequent intervals* day and night (2) the *cold pressor test* consisting of immersing one hand in ice cold water at 40 F for 30 to 60 seconds which will cause a mean rise of over 30 mm of mercury in systolic pressure and of over 25 mm in diastolic pressure in hypertensive individuals or somewhat less in hyperreactors (who may some day become hypertensive) and much less in normal nonhypertensive persons (Hines and Brown 1936) (3) the *sedation test* consisting of the effect of extreme sedation by the ingestion of 3 gr of Sodium Amytal every hour for three doses the blood pressure dropping to normal in the early or mild and labile cases and (4) the *postural test* the diastolic pressure rising in hypertensive cases 15 to 30 mm with less change in the systolic level and hence a drop in pulse pressure readings on assuming the erect position

A very high diastolic pressure is a bad sign and a constant finding of such a pressure over 130 mm of mercury means that without special treatment but a few months or years of life remain The auscultatory gap found by the auscultatory method of sphygmonanometry (discussed in Chapter 6) and pulsus alternans (to be discussed in Chapter 30) are both common in hypertension and appear during blood pressure studies The blood pressure should be measured in spite of the presence of atrial fibrillation an approximate figure so obtained is generally sufficiently accurate When hypertensive crises occur due to adrenal medullary tumors (pheochromocytomata) or to vasomotor (arteriolar constriction) storms in the course of chronic hypertension sometimes with serious effects such as apoplexy the blood pressure may suddenly rise 50 to 100 or more millimeters systolic and half that diastolic

Special tests for a *pheochromocytoma* have been developed consisting of sharp increase of blood pressure on administration of histamine Mecholyl or tetraethylammonium chloride no reaction to epinephrine and reduction of blood pressure on intravenous injection of benzodioxane The more established tests are those with histamine (Roth and Kvale 1945) and benzodioxane (Goldenberg Snyder Aranow 1947) The former test consists of determining the basal blood pressure and pulse records after recumbency for ½ to 1 hour then every minute for 15 minutes after the intravenous injection of 0 025 to 0 05 mg of histamine (0 25 to 0 5 cc of 0 01 per cent solution in normal saline) a positive reaction is shown by a sharp rise of blood pressure of 100 mm or more in the presence of a pheochromocytoma in contrast

to a much slighter rise in a case of essential hypertension The severity of this reaction has resulted generally (except when the blood pressure is not much elevated to start with) in replacement by the benzodioxane test, which consists of the intravenous injection in 2 minutes via a normal saline drip (in operation for 20 to 30 minutes before the test) of 0 25 mg per kilogram body weight in 1 per cent solution of piperidymethyl benzodioxane (933 F) an adrenolytic or epinephrine antagonistic substance a positive reaction *consists of a considerable fall in both systolic and diastolic pressures in the* course of a few minutes Less satisfactory testing for a pheochromocytoma includes perirenal air insufflation which can be difficult and dangerous and nondiagnostic in some cases when the tumor is situated not at the adrenal gland but elsewhere along the sympathetic chain as it sometimes is

Roentgen ray examination in hypertensive heart disease shows cardiac enlargement chiefly of left ventricular type (Figure 96 illustration below) and



FIG 96 Roentgenogram showing a moderately enlarged hypertensive heart with prominence of the left ventricle The arc of the descending aorta is well seen above the heart shadow because of its increased density (arteriosclerosis) The pulmonary artery is not enlarged there has been no pulmonary vascular congestion

general dilatation of the aorta with prominence of both ascending and de scending portions in the thorax Later in the disease when left ventricular failure begins greater cardiac enlargement is found due to dilatation and to involvement of the right side of the heart and of the left atrium then the lung hilus shadows and the pulmonary artery shadow tend also to be prominent in keeping with the newly developed hypertension in the pulmonary circula tion

Electrocardiography often shows no abnormality in hypertensive heart dis ease but in the majority of chronic cases there is characteristic hypertensive pattern (Figure 97A) consisting of lowering to inversion of the *T* waves in Lead 1 and in the leads over the left ventricle (V_4 V and V_6) and of in

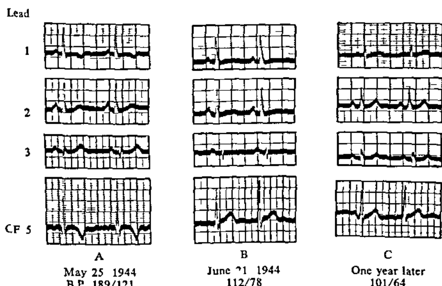


FIG 97 Reversal of the hypertensive electrocardiographic pattern after lumbodorsal sympathectomy Male age 39 Lumbodorsal sympathectomy right side May 31 1944 left side June 9 1944

creased amplitude of the *R* waves in these same leads there is frequently also left axis deviation as found in the classical bipolar limb leads although a horizontal heart position commonly found in hypertensive patients is more responsible for such axis deviation than is left ventricular enlargement It is likely that dilatation in addition to hypertrophy of the left ventricle is respon sible for this abnormality of the electrocardiogram as borne out by the return to a more normal record in some cases when the hypertension and left ven- tricular strain therefrom are relieved by splanchnic resection (Figure 98 page 487) Arrhythmias are not the rule but when they appear they are well shown in the electrocardiogram

Course and prognosis Hypertensive heart disease tends to be a progressive condition leading sometimes rapidly but usually slowly to congestive heart failure in the course of 10 to 20 years The condition begins as a rule in-

sidiously and very gradually in middle life at about forty to fifty years of age and is often discovered in the course of routine blood pressure or cardiac examination (for life insurance for example) When it begins in youth it is more serious when it begins in old age it is not so serious unless coronary disease or cerebral arteriosclerosis complicates the condition Sometimes at first there are merely waves or periods of hypertension with normal pressure between Transient or paroxysmal hypertension may however in the course of time do as much harm to some patients as sustained hypertension in the usual run of cases Even when the hypertension becomes fixed there tend to be waves or periods of considerable increase above the average level for example a systolic pressure of 180 mm may rise to 240 for a few hours at a time on excitement fatigue or from unknown cause There may be a mild and temporary increase of blood pressure or an exacerbation of a pre-existing hypertension at the time of the menopause

The term *malignant hypertension* has been introduced to designate an extreme grade of hypertension with a rapidly fatal course (months to a year or two) Actually however it includes a variety of severe cases those that are marked and serious from the very beginning (usually young adults), those approaching the end of a long hypertensive course and those who after some years of a fairly benign hypertension take a rather abrupt turn for the worse The chief characteristics of malignant hypertension are the high diastolic blood pressure (130 to 140 mm or over) the very abnormal eye grounds and the bad prognosis and rapid course

Although heart failure is the most common of the end results of hypertension cerebral hemorrhage is also frequent angina pectoris and coronary thrombosis are next in order and renal insufficiency is least common In a series of 410 cases of primary or essential hypertension examined post mortem (Bell and Clawson 1928) congestive heart failure was found in 187 cases (44½ per cent) cerebral hemorrhage or thrombosis in 81 cases (19 per cent) coronary heart disease in 67 (16 per cent) renal insufficiency in 36 (8½ per cent) and miscellaneous conditions in 49 (12 per cent) In a later series (1941) of 2 597 hypertensive patients who succumbed to cardiovascular disease Clawson found that death was caused by myocardial insufficiency in 43 3 per cent by coronary heart disease in 36 per cent by cerebral hemorrhage in 13 9 per cent and by renal insufficiency in 6 8 per cent In the series of 375 hypertensive cases studied by Murphy and his associates (1932) heart failure (mostly congestive but including coronary) caused 50 per cent of the deaths, infections 14 2 per cent apoplexy 13 4 per cent and renal failure 10 4 per cent Fahr (1935) put the percentage of deaths in hypertensive cases due to congestive heart failure at 55

Serious prognostic signs are very high diastolic blood pressure (over 130 mm) marked changes in the eye grounds pulsus alternans gallop rhythm and paroxysmal dyspnea or cardiac asthma A serious prognosis should not be given on the finding of slight or moderate hypertension or slight cardiac

enlargement alone Much cardiac enlargement or sustained hypertension of very high degree warrants a grave prognosis

On the other hand within the last decade a change has taken place in the course and probable prognosis of some of the cases of hypertension even of high grade with hypertensive heart disease as the result of the more complete splanchnic sympathectomy carried out by Smithwick (1940 and observations made by myself on his cases 1942–1951) Occasionally striking results have occurred with relief not only of the hypertension eye ground changes and symptoms but also of the physical and electrocardiographic evidences of the heart strain such as gallop rhythm pulsus alternans and *T* wave abnormalities In at least a few of these cases the hypertensive heart disease should be regarded like the thyrotoxic hearts and some instances of acute rheumatism as a reversible process in its acute or subacute stage The strict application of low sodium and of Kempner s rice diets has also reversed or retarded the *hypertensive process in some though relatively fewer cases*

Complications The most important complications of hypertensive heart disease and their relative frequency have been noted above congestive heart failure apoplexy angina pectoris coronary thrombosis and nephritis with uremia Acute infections are common and may end the story as may also pulmonary embolism from phlebothrombosis in the leg especially after congestive heart failure has set in Arteriosclerosis is almost universally found in older patients with hypertension but although undoubtedly favored by the strain of the high blood pressure it is not by any means a constant finding Types of heart disease other than that due to coronary sclerosis may complicate the enlargement and weakness from hypertension Syphilitic aortitis thyrotoxicosis and rheumatic heart disease are not infrequent complications Hypertension is often found with aortic regurgitation and with mitral disease with or without much stenosis and it is not rare even with aortic stenosis Finally nervousness and neurocirculatory asthenia are common complications of hypertensive heart disease and frequently exaggerate the seriousness of the symptoms and of the condition itself

Treatment The treatment of hypertensive heart disease resolves itself into three parts consisting of (1) the therapy of cardiac complications (2) the therapy of the underlying hypertension and (3) preventive measures to protect the damaged heart

(1) The treatment of the cardiac complications such as congestive failure cardiac asthma angina pectoris coronary thrombosis and atrial fibrillation will be discussed in later chapters of this book mainly in Part IV The presence of hypertension does not in any way contraindicate the usual measures as for example the use of digitalis for failure or for atrial fibrillation of nitrites for angina pectoris of morphine for coronary thrombosis and cardiac asthma and of quinidine for atrial fibrillation It need hardly be added that the most important measure of all not in the emergency but when the emergency is over is an attempt if it seems feasible by medical or surgical measures

(outlined below) even in the absence of specific therapy to reduce the main factor of strain namely the hypertension

(2) The treatment of the hypertension itself continues to be a difficult task in the present state of our knowledge but important studies in progress offer much hope for the future

Drugs Many measures especially medicinal to reduce high blood pressure have been suggested and tried sometimes with slight temporary success some times with toxic effects sometimes though rarely with prolonged benefit these include such drugs as the nitrites bismuth subnitrate benzyl benzoate atropine calcium chloride potassium iodide bromides parathyroid preparations theobromine theophylline ethylene diamine (called also aminophylline, and formerly Euphyllin or Metaphyllin), theobromine sodiosalicylate (Diuretin) theobromine sodium acetate (Thesodate) and other diuretics cucurbocitrin (*from watermelon seeds*) papaverine mistletoe (*intrait de gui*) sunflower seeds garlic yohimbine liver extract ovarian extract testosterone chloral hydrate and other sedatives or hypnotics like phenobarbital (Sodium Luminal) cathartics sulphur and the sulphocyanates (thiocyanates) of sodium or potassium In one series of 70 patients with established essential hypertension (Evans and Loughnan 1939) the effects of 33 different preparations and of a placebo on the blood pressure and on the symptoms were observed None produced a satisfactory hypotensive effect Symptomatic improvement greater than that resulting from the placebo followed the use of only six of the drugs namely bismuth subnitrate iodine and iodide bromide Sodium Luminal (phenobarbital) Theominal (theobromine and phenobarbital) and potassium thiocyanate The sedative drugs seemed to have value in temporarily relieving nervous symptoms when these were prominent and since it is now well established that heavy sedation (e g, Sodium Amytal 0 2 gm 3 gr every hour for three doses) frequently reduces hypertensive blood pressure readings markedly even to normal there is an additional good reason therein for the therapeutic use of sedative drugs

There has been in recent years a revival of the use of the thiocyanates (sulphocyanates) and of veratrum viride and various of its derivatives which appear to be more effective in reducing the blood pressure and in relieving symptoms in hypertensive patients than do other drugs However their effect has been often disappointing and sometimes seriously toxic They should be used under close observation best controlled in the case of the thiocyanates by frequent measurements of the concentration of the drug in the blood itself (preferably kept at 6 to 12 mg per 100 cc blood)

Veratrum viride has been in use for many years in the treatment of eclampsia frequently with considerable reduction of blood pressure but complicated by toxic symptoms The drug under various trade names has been in use also for some time in the treatment of essential hypertension with similar results An analysis of its effects has been published by Freis and Stanton (1948) Only recently have satisfactory extracts been made from veratrum in the form of purified alkaloids One of these called protoveratrine from Vera

trum album has given much promise as indicated by its uniform reduction of both systolic and diastolic pressures for several hours at a time without serious toxic symptoms in hypertensive animals and man when given parenterally (Meilman and Krayer 1949) More recently still protoveratrine has been given orally to ambulatory patients with beneficial effects over periods of weeks and months but the dosage has to be very carefully regulated for each individual to obtain the best hypotensive effect with the least toxic result The dosage parenterally varies from 0 25 to 1 0 mg every 6 hours and orally from 0 5 to 2 0 mg every 8 hours This drug has proved to be especially useful in patients who are too old or otherwise unsuitable for lumbodorsal sympa thectomy Whether or not protoveratrine or some other even more effective medicament can actually replace operative treatment it is too early to say It should be added that the heart rate as well as the blood pressure is considerably reduced by veratrum derivatives even down to 40 per minute

Other derivatives from veratrum viride that have been used somewhat helpfully in cases of hypertension are Vertavis (15 to 30 Craw units daily) and especially Veriloid which can be given in the dosage of 2 to 3 mg orally every 6 hours (Wilkins Stanton and Freis 1949 Connar Emlet and Grimson 1950) It may be added that atropine should be available to counteract toxic effects from any veratrum preparation

Potassium thiocyanate is conveniently given in the form of a 4 to 8 per cent solution in peppermint water or in a simple syrup such as that of sarsapa rilla and in the dosage of one teaspoonful (4 cc) containing 0 16 to 0 32 gm (2½ to 5 gr) three times a day (total of 0 5 to 1 0 gm or 7½ to 15 gr) the dosage varies as circumstances warrant In one of the largest group of cases reported that of 246 by Barker and his associates (1941) symptoms were relieved and blood pressure was reduced in 47 5 per cent in the course of two to four weeks In another series of 50 patients subjec tive improvement was definite in 63 per cent fair in 20 per cent and dis appointing in 17 per cent six showed toxic effects the blood pressure of every patient was somewhat reduced and objective results were considered satisfactory in 78 per cent fair in 16 per cent and poor in 6 per cent the average systolic pressure dropped from 197 mm before treatment to 156 mm with treatment and the average diastolic pressure dropped from 115 to 94 the average maintenance dosage of 5 gr varied from three to twenty-one (aver age nine) times per week In another group of 20 patients with pronounced arterial hypertension (Blaney Geiger and Ernst 1941) to whom potassium thiocyanate was given after a control period on placebos one half of the total number apparently responded with a complete or partial remission of their hypertension eight of the 16 patients with symptoms felt better during the therapy a few felt worse In still another group 120 hypertensive patients were treated (Caviness and associates 1941) with results recorded as good in 68 9 per cent (reduction of more than 15 per cent in both systolic and diastolic pressures) fair in 11 5 per cent and poor in 19 6 per cent Other authors however have emphasized the toxic effect of the drug (Wald Lindberg and

Barker 1939, Robinson and O Hare 1939), the last named authors reported toxic symptoms in 29 (38 per cent) of their 75 patients less serious in 23 of them (nausea, weakness dermatitis purpura and a decrease in libido) and more serious in the other 6 (dermatitis exfoliativa congestive heart failure cerebral thrombosis angina pectoris and psychoses), but at the same time they believed that there was decided value in the therapy when carefully controlled (maximum drops in blood pressure of over 100 mm systolic and 35 mm diastolic were observed in 3 cases, average drops of 40 mm systolic and 20 mm diastolic in 63 per cent of the patients and relief of hypertensive headaches in 18 out of 20 cases)

Rogers and Palmer (1947) compared the use of thiocyanate therapy in hypertension to sympathectomy by Smithwick s operation, they found that only about one fifth of 100 patients showed any considerable fall in blood pressure from the effect of the drug and that such falls required continuous therapy for their maintenance and were not at all comparable to the drop in pressure obtained in favorable cases by splanchnic resection once in a while however the drug produced brilliant results in the relief of headache

Recent papers on the administration of the thiocyanates emphasize a general dissatisfaction with their use (Ruskin and McKinley 1947) and their greater value in the absence of organic changes (Alstad 1949)

Other drugs more recently introduced with definite hypotensive but generally disappointing effects include tetraethylammonium chloride dihydroergocornine derived from ergot Dibenamine and Driscol Still other medicaments recently recommended but unconfirmed include procaine HCl in honey thyroid extract and Rauwolfia serpentina Rutin a flavone rhamnoglucoside extracted from wheat germ has been used to reduce the hazard of hemorrhage from capillary fragility in essential hypertension but there has been considerable doubt as to its clinical value

Most recently hexamethonium salts have been tried for hypertension (Smirk 1951, Locket et al, 1951 George W Pickering personal communication 1951) it appears to be effective if given intramuscularly 3 or 4 times a day at increasing dosage beginning with 15 mg

Diet Dietary restrictions have been tried particularly the limitation of the total caloric value of the diet of protein food and of common salt Reduction of weight has been carried out with some benefit in a good many obese patients reference has already been made earlier in this chapter (page 468) to the hypotensive effect of starvation with resulting loss of weight.

Two special diets are in common use today in the treatment of hypertension because of their success in some though in the minority of cases One of them introduced years ago emphasized the need of restriction of sodium chloride (Allen 1920) and has been resumed and studied in recent years with variable success It has been shown that it is the sodium content of the diet that is important as it is in the case of the dietary treatment of congestive heart failure in fact it is the hypertensive patient with congestion threatened or present who receives the most benefit Just how on occasion the sodium re

striction acts on hypertension has not yet been elucidated its relationship to adrenal function among other mechanisms has been indicated

The other diet which in recent years has been much utilized in the treatment of hypertension is the rice diet introduced by Kempner (1944) In the first place this diet has about as low a sodium content as it is possible to give (less than 0 5 gm) secondly it is very low also in protein (about 20 gm daily) and thirdly it contains very little fat (about 5 gm daily) It consists of rice fruit and sugar with no other food during the first six weeks or more of treatment but later is liberalized according to circumstances The explanation of its success is still unclear but in those persons who are faithful to it (a minority of cases) there is an improvement of abnormal eye grounds electrocardiogram and heart size and a definite reduction in blood pressure both systolic and diastolic in more than half (the exact percentage has not yet been determined) whether or not there has been a loss of weight There need be no weight loss since the diet contains at least 2 000 calories As in the case of the low sodium diet so here too it is the somewhat congested hypertensive patient who seems to receive the most benefit and also some cases of renal involvement for whom as a matter of fact the diet was first introduced

It should be emphasized that the conscientious following of this rice diet' has been helpful in the case of many hypertensive patients including some not improved by other therapeutic measures medical or surgical including sympathectomy also that it can be added helpfully to other treatment not sufficiently effective per se

Much study remains to be done on the effect of diets on hypertension and it is to be observed also that on occasion there may develop from either of the diets noted above a serious sodium lack requiring emergency treatment

Other medical measures Measures of physical therapy have been advocated rest physical and mental baths of all kinds venesection electrotherapy (high frequency diathermy) and roentgen ray irradiation of the pituitary and adrenal glands Psychotherapy has been used both consciously and unconsciously along with attempt to adjust or to remove strain of professional or business life of family affairs and of social activities Often these measures have been combined in various ways and degrees particularly at special health resorts or spas and often by the family doctor or specialist at home

The imposing list of remedies and their advocacy by so many different persons reveal their very weakness we have not yet a real cure or a specific treatment for hypertension except on the one hand surgical removal of certain unilaterally diseased or deformed kidneys and pheochromocytomata in rare cases and on the other hand thoracolumbar (lumbodorsal) sympathectomy in suitable cases Whether to match the numerous causes of hypertension we may have to develop a variety of cures or whether a single drug or chemical or other measure will neutralize hypertension in the majority of cases no matter what the original cause we do not yet know

Rest either per se or enforced by a stay in a hospital or in bed at home as the result of some illness or surgical operation sometimes materially lowers

a high blood pressure even temporarily to normal if it is not too high to start with but rarely is this effect maintained after the patient has become active again in contrast to the more lasting effect of lumbodorsal splanchnic resection when it is successful as will be recounted below (Rojas et al 1944)

Summarizing the value of the various methods of medical treatment it may be said that a few have been shown to be more useful than others, not as cures but in a palliative way These are (1) a relief from all avoidable nervous and physical strain sometimes in the form of 'rest cures but not an interdiction of moderate healthy outdoor exercise (2) a general reduction of diet not to a weakening starvation level but to one that prevents gain of weight or causes a moderate gradual loss of weight if there is obesity as there so often is in hypertensive cases and especially a reduction of sodium intake as in the rice diet (see above) (3) symptomatic or specific treatment of any particular complicating diseases or disorders including the eradication of such foci of infection as apical tooth abscesses (4) the trial of nerve sedatives and (5) the use of the more successful drugs namely potassium thiocyanate and especially the Veratrum derivatives under careful control as already described Sometimes none of these measures has any effect whatsoever Slight oscillations of blood pressure must not be regarded as important indications of the effect of treatment Relief from all avoidable nervous and physical strain with a healthy regulation of rest, exercise diet and bowel action is of prime importance and sometimes not possible at home where business social and family cares are hard to escape A holiday in some pleasant place or a visit to a good health resort at home or abroad may do much good under such circumstances But whether carried out at home or at a health resort a fall in blood pressure though rarely to normal levels not infrequently follows such therapy

Surgery In late years there have been introduced for the treatment of hyperpiesia certain surgical procedures Decortication of the kidneys has proved ineffective Excision of a deformed or diseased kidney (especially the site of cystic or pyelonephritic degeneration) with the other kidney fairly normal has cured the hypertension in a few cases justifying though to a small degree only the hopes from such a procedure based on the effect of the vascular clamp in experimental animals pleas have been made for conservatism in such surgery so that useful renal tissue may not be sacrificed in vain Extensive bilateral thoracic and lumbar rhizotomy though reported to be effective is too serious and dangerous an operation The value of adrenal denervation and of subtotal adrenalectomy is now being investigated A few spectacular cures have resulted from the exploratory discovery and removal of adrenal tumors (especially the pheochromocytoma responsible for severe paroxysmal hypertension)

Sympathectomy including *splanchnic nerve resection (bilateral)* introduced with the idea of causing a drop in blood pressure as the result of splanchnic and lower limb arteriolar dilatation has been developed to a high degree by a number of surgeons (Peet and associates 1935 1940 1948 Adson and Allen 1940 Smithwick 1940 1948 de Takats and associates 1942

1948 Crutchfield 1947 Poppen 1947 Grimson and Orgain 1948) some of whom most notably Smithwick now denervate both above and below the diaphragm with the result that more and more patients have secured and maintained a distinct hypotensive effect (so great in some cases that at first syncope or near syncope may occur in the erect posture) Smithwick (1940 1942) stated that removal of virtually the entire great splanchnic nerve with division of all of its aortic branches coupled with interruption of the communicating rami of D9 D10 D11 D12 and L1 together with excision of the sympathetic trunk over this area is the minimal procedure found consistently to produce a blood pressure change which is characteristic of a thorough interruption of the nerve supply to the splanchnic bed The younger patients with more labile vasopressor reactions smaller pulse pressures with relatively higher diastolic than systolic levels and less permanent cardiovascular damage have been found most amenable to improvement even though their pressures may be elevated and their fundi seriously affected (and as such belonging to the malignant hypertensive category) Spectacular improvement (perhaps cure) has been noted now in a good many cases but the procedure is still relatively new and has but recently emerged from the experimental stage

Among 224 cases sympathectomized at the Mayo Clinic (Allen and Adson 1940) good results were reported in 13 per cent fair in 18 per cent temporary in 39 per cent and poor in 30 per cent With improved technic consisting for the most part of more extensive sympathectomy better results have been obtained since 1940 Among the larger series of cases treated by experienced surgeons and with better selection than originally the results have been well worthwhile in slightly over half the patients operated upon and followed for several years For example in Smithwick s series of 256 patients with essential including malignant hypertension operated upon by his newer technic between 1938 and 1943 and followed for five to nine years the total mortality was 31 2 per cent distinctly less than the expected rate for similar hypertensive cases not so treated 90 per cent of the survivors were improved symptomatically the eye grounds were improved in 41 per cent the electrocardiograms were better in 42 per cent and the blood pressures were lower in 47 per cent (Smithwick 1948) During the first five year follow up study 84 per cent of the cases had shown a distinct lowering of pressure but a considerable number of these showed a gradual return of blood pressure toward or to the preoperative levels during the later (5 to 9 years) follow up period Palmer (1947) reported a diminishing return of favorable results the longer the patients are followed nearly 70 per cent early in his experience declining to 25 per cent when patients are followed three to five years or more But he writes this effect has been obtained twice as frequently in this series by surgical means as by a careful medical regimen and was obtained in patients with malignant hypertension whose blood pressures were unaffected by medical management Isberg and Peet (1948) have reported that 60 per cent of 384 cases of arterial hypertension were alive 5 to 12 years after splanchnicectomy of the survivors 41 per cent of those with abnormal electrocardiograms showed improvement and 44 per cent of those with preoperative

cardiac enlargement showed significant decrease in heart size Another series of 100 consecutive patients were treated by extensive thoracolumbar sympathectomy by the same surgeon and carefully followed for 1½ to 4 years after operation the results were good in 47 per cent fair in 24 per cent and unsatisfactory in 28 per cent, including one operative death and six others who died after discharge from the hospital (Poppen and Lemmon 1947) Grimson and his associates (1949) have reported the results of subtotal to total sympathectomy in 113 patients with severe or moderately severe hypertension followed for one to nine years, 97 of the cases were still living with normal or near normal blood pressure in 31 reduced pressure in 43 more and postural lowering of pressure in all together with improvement in eye grounds in many cases and in electrocardiograms and heart size in a few

I myself have seen many excellent results among the cases sympathectomized by Smithwick not only have the eye grounds cleared and the pressure fallen to normal or near normal but evidences of heavy strain on the heart have also abated including electrocardiographic abnormalities (Figure 97 page 477) (Canabal Thomson and White 1944 White et al 1945) and even on occasion x ray evidence of cardiac enlargement (White 1946 and Figure 98) My own most interesting experience in the treatment of serious hypertensive cardiovascular disease has been summarized in a personal study of 100 cases with important complications including for the most part left ventricular weakness or frank failure but also cerebral vascular lesions angina pectoris and past myocardial infarction Fifty of these cases had thoracolumbar sympathectomy by Smithwick the other cases (controls) of similar sex and age distribution (ratio of 3 men to 1 woman and large majority of cases under the age of 50 in each group) and with similar defects had medical but not specific dietary treatment Each group was followed for a minimum of three years The mortality in a given period of time of the surgical group was less than half that of the medical group and the blood pressures eye grounds electrocardiograms and symptoms were normal or much nearer normal in the majority of the survivors of the surgical group than in the controls The surgical cases who were not helped at all or who were worse or died were further analyzed one patient who had been improved died later of leukemia while 12 of the other 29 cases who died or were not improved could in retrospect have been quickly rejected for sympathectomy by the application of new criteria recently introduced by Smithwick (1950) in which a scoring of adverse points for various abnormalities is made and then the points added up (scores under 4 more suitable for operation than those above) For example an abnormal electrocardiogram is one adverse point x ray evidence of cardiac enlargement another age of 50 years a third and so on Abnormality of renal function is especially serious and in general a contraindication to surgery moderate involvement of the heart however or a cerebral vascular lesion is not a bar per se The borderline group (Smithwick s Group 3) contained 19 of my 50 sympathectomized cases 10 of which turned out well and 9 poorly it is now this group that especially needs further evaluation

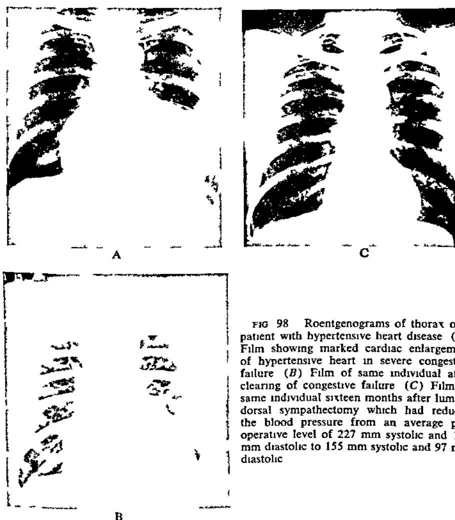


FIG 98 Roentgenograms of thorax of a patient with hypertensive heart disease (*A*) Film showing marked cardiac enlargement of hypertensive heart in severe congestive failure (*B*) Film of same individual after clearing of congestive failure (*C*) Film of same individual sixteen months after lumbo-dorsal sympathectomy which had reduced the blood pressure from an average pre operative level of 227 mm systolic and 120 mm diastolic to 155 mm systolic and 97 mm diastolic

The fact that 5 of my 50 hypertensive cases with grave cardiovascular lesions were perfectly well with normal blood pressure three years or more after operation and that 15 more were distinctly improved is quite clear proof in my experience that hypertensive cardiovascular disease is reversible and that up to the present time sympathectomy has achieved the greatest thera peutic success in this respect

It must be clearly recognized however that this surgical treatment is largely empirical and may be replaced or reinforced later by something better that it is a serious major operative procedure in itself (in fact two operations first on one side and then on the other ten days to two weeks apart) that it is followed by a tedious often uncomfortable convalescence lasting two or three months and that it is not suitable for the majority of patients with hyperten

sion Many cases are too old (an age under 50 years is desirable), some patients are too sick (especially if they have important kidney disease or renal insufficiency) some cases are too mild (with mostly a nervous or transient hypertension which should be watched) and many cases have mostly an arteriosclerotic hypertension with high systolic pressure (over 200 mm) and relatively low diastolic pressure (about 100 mm) allowing long survival and not requiring or appreciably helped by sympathectomy But for particular cases especially young and middle aged men with malignant hypertension and good renal function sympathectomy can be lifesaving Such indication applies of course to well under 10 per cent of all hypertensive patients

Thus as I stated seven years ago in the third edition of this book Smithwick s work represents a notable advance in the control of hypertension though we may hope that some simpler therapy or preventive measure will eventually replace operative treatment

Finally it must be said that a survey of many cases showing the serious late effects of chronic hypertension makes it evident that early discovery of hypertension at its origin by annual examinations affords the only promise for control of the disease by the earliest application of the measures outlined above until someone discovers a specific, perhaps antitoxic, cure Such a cure is being sought in the work of Page and his colleagues (1940 1949) Ferris et al. (1948) Goldblatt (1948) Schroeder (1948) Krayer and Meilman (1949) Wilkins (1949), Smithwick (1949), Chasis Goldring and Smith (1949) and many others The work is, however very arduous and difficult and much patience must be exercised in awaiting the final results

(3) The care of a patient with hypertensive heart disease aside from the treatment of cardiac complications and hypertension already mentioned is like that of any chronic cardiac patient a reasonable restriction of activity and nervous strain common sense as to diet exercise and rest occasional or frequent leisurely holidays regulation of bowels, avoidance of excessive use of alcohol tobacco coffee and tea and the eradication of focal infection It is however of the greatest importance to recognize the possibility of the reversibility of even serious hypertensive heart disease by therapy at present best exemplified in the surgical procedure of sympathectomy

Finally it is of prime importance to practice preventive medicine in hypertensive families by instructing both young and old concerning the establishment of sensible health habits

Differential diagnosis Hypertensive heart disease is generally easy to recognize because of the presence of hypertension and of cardiac enlargement without valvular disease The onset of dilatation of heart and aorta sufficient to cause mitral and aortic systolic murmurs the occurrence of atrial fibrillation the masking of the original condition by the presence of marked congestive heart failure and especially the fall of blood pressure to normal levels may make it very difficult or even impossible to distinguish some cases of hypertensive heart disease from chronic coronary heart disease in which the history is atypical or obscure and from cardiac enlargement and failure due to

thyrotoxicosis or even to chronic rheumatic or syphilitic valvular disease A careful history to rule out rheumatic and syphilitic infections knowledge of physical examinations in the past which have not shown evidence of valvular disease or thyrotoxicosis and especially careful inquiry as to a previous discovery of hypertension are often more essential in this differential diagnosis than are physical examination and laboratory tests carried out at the moment when the decision must be made

HYPOTENSION

Hypotension that is a systolic blood pressure below 100 mm of mercury does not cause heart disease although it sometimes accompanies it as in the case of aortic stenosis or acute heart failure from cardiac infarction (due to coronary thrombosis) Low blood pressure is more commonly found in the absence of heart disease than in its presence especially in certain weak and frail individuals in chronic wasting disease temporarily in peripheral vascular failure or shock (see Chapter 31) or in attacks of neurocirculatory asthenia or of paroxysmal tachycardia with excessively rapid heart rates in a few cases of marked carotid sinus reflex in the rare cases of adrenal (Addison s) disease and in a few individuals as a postural phenomenon where it has been called orthostatic or essential hypotension

Postural hypotension has been called a disease of the sympathetic nervous system by Stead and Ebert (1941) whether peripheral or central is not clear though the latter is favored (Hermann 1947) Patients with this condition do not apparently pool more blood in the lower part of the body on standing than do normal subjects but they lack the reflex vasoconstriction which maintains the arterial pressure in normal subjects when erect this phenomenon may appear acutely and temporarily in healthy persons after very strenuous exercise (Eichna et al 1947) and it is of course quite common for a few weeks after thoracolumbar sympathectomy for hypertension

An abdominal support elastic stockings paredrine (Yukis and Griffith 1948) and angiotonin and the head up bed (Corcoran et al 1942) have given relief

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CHAPTER 20

PULMONARY HEART DISEASE
ACUTE AND CHRONIC COR PULMONALE
PULMONARY HYPERTENSION

Introduction During the past seven years since the publication of the third edition of this book there have been distinct advances both in the clinical recognition of the frequency of pulmonary embolism in medical especially cardiac cases along with better diagnostic criteria and also in the introduction of preventive measures thus reducing the incidence of the complication of the acute cor pulmonale Also the application of improved industrial hygiene and of more specific measures to reduce pulmonary infections will doubtless result in time in a decreased incidence of the chronic cor pulmonale

The effect of pulmonary hypertension on the right ventricle is comparable to that of systemic hypertension on the left ventricle except that in the case of the pulmonary circulation there are more instances of *sudden unexpected* great increase in blood pressure to cause acute right ventricular strain Pulmonary hypertension originates in the great majority of cases in seven different ways in the first place and most commonly from dilatation and failure of the left ventricle abrupt or gradual secondly and fairly often from mitral valve deformity with or without stenosis thirdly and also frequently and always abruptly from massive pulmonary embolism fourthly and usually to but a slight extent from chronic pulmonary disease including fibrosis and emphysema fifthly importantly but not often from the pressure of inhaled dust in particular silica sixthly from the more marked grades of chest deformity due to high degrees of kyphoscoliosis or compression (not displacement) of the heart by the funnel chest and finally and rarely from primary disease of the pulmonary arteries and arterioles There are also excessively rare instances of acute subacute or chronic cor pulmonale secondary to obstruction of the pulmonary circulation by metastatic malignancy or by high degrees of diaphragmatic herniation with compression of the thoracic contents by stomach and intestines

The first factor left ventricular dilatation and failure will be discussed in

Chapter 30 on Congestive Heart Failure the second factor mitral valve deformity will be discussed in Chapter 26 on Valvular Disease The third factor pulmonary embolism in its relationship to the heart will be discussed in the present chapter under the heading *the acute cor pulmonale* The fourth factor chronic pulmonary disease if extensive and prolonged enough gives rise to a cardiac condition which used to be called the emphysema heart but which along with the cardiac effect from the fifth sixth and seventh factors namely pneumoconiosis marked thoracic deformity and pulmonary endarteritis obliterans will be discussed below under the far superior designation *chronic pulmonary heart disease* or *the chronic cor pulmonale*

Incidence This condition—cor pulmonale or pulmonary heart disease—is an important one, though variable in incidence in different parts of the world It has been considerably neglected and is probably more common than most statistical studies at present indicate especially since it occurs so often in older people who are not frequently seen in general hospitals which treat acute conditions In New England its chronic form was noted 21 times (0 9 per cent) in 2 314 cases of organic heart disease (White and Jones 1928) but in certain places like Vienna (Erdheim personal communication 1929) and Cleveland (Scott 1941) it is either more common or better recognized Scott noted it in 6 8 per cent of 790 cases who died of heart disease in Cleveland Two groups of cases of chronic cor pulmonale studied at autopsy have been recently reported 60 by Spain and Handler in 1946 and 42 by Spatt and Grayzel in 1948 Of 123 collected cases analyzed by Sodeman (1948) 75 were associated with emphysema 14 with bronchial asthma 13 with silicosis 5 of which had also tuberculosis 9 others with tuberculosis 7 with bronchiectasis and 1 each with kyphoscoliosis pulmonary arteriosclerosis pulmonary fibrosis and schistosomiasis The incidence of the acute form is more common than was previously recognized being found in about 10 per cent of cases of acute pulmonary embolism but is probably present in additional cases though masked by other signs e g coronary insufficiency In slight degree it is not uncommon in high degree it appears to be rather rare

ACUTE AND SUBACUTE COR PULMONALE

Etiology *Cause* Sudden massive obstruction of the pulmonary circulation sufficient to cause dilatation of the right ventricle gives rise to the condition which we have called *acute cor pulmonale* (McGinn and White 1935) The cause of such sudden massive obstruction of the pulmonary circulation is in the great majority of cases extensive pulmonary embolism originating from systemic venous thrombosis usually in the leg veins Conceivably a large embolus may also come from the right atrium but this is much less common as is likewise embolism from pelvic and abdominal veins Sudden perforation of an aortic aneurysm into the pulmonary artery can raise the pulmonary arterial pressure so abruptly that doubtless acute dilatation of the right ventricle antedates the inevitable death that ensues Also an acute compression of

the lungs by a sudden increase of a herniation of the abdominal contents through the diaphragm has been reported as a cause of the acute cor pulmonale (McGinn and Spear 1941), as has likewise acute spontaneous mediastinal emphysema (Klein 1947) Pneumonia and other pulmonary infections do not give rise to the acute cor pulmonale

Age The acute cor pulmonale is found in the great majority of cases in older persons that is in just those most subject to pulmonary embolism it is rare under 35 years of age

Sex Both sexes are about equally affected

Predisposing factors By far the most important predisposing factor is systemic venous thrombosis in the deep veins of the calf leading to involvement of the femoral veins or in the long saphenous veins whence multiple and often lengthy emboli are carried to the lungs favoring such thrombosis are stasis and phlebitis in individuals who have had a surgical operation (especially an abdominal or pelvic operation) or an accident or leg injury or any prolonged illness within a few weeks of the time of the occurrence of the pulmonary embolism Flabby musculature a prolonged cramped position especially seated with pressure under the knees and poor local circulation in the legs increase the likelihood of a venous thrombosis and pulmonary embolism under the conditions just mentioned

Pathology The only characteristic pathologic findings in the case of the acute cor pulmonale are dilatation of the pulmonary artery dilatation of the right ventricle and obstruction of the pulmonary artery or arteries usually by a single coiled massive embolic thrombus but sometimes by multiple emboli There must be a sudden blocking of at least 60 per cent of the pulmonary arterial circulation before the normal right ventricle dilates appreciably to effect this there must be either a large rider embolus at the bifurcation of the pulmonary artery or at least two large emboli one in each lung

There may or may not be congestive heart failure complicating the right ventricular dilatation At autopsy there may be little or nothing found wrong with the right heart because of the possibility of rapid subsidence of the functional cardiac dilatation especially if death has resulted finally from a state of vascular shock

Careful search at postmortem examination will almost always reveal extensive thrombosis in a long leg vein most often the superficial femoral or the saphenous which is frequently not evident during life

Symptoms There are no particular symptoms of the acute cor pulmonale per se except that some of the substernal oppression that attends the acute pulmonary embolism or resulting coronary insufficiency in an older person may possibly be attributed to the acute cardiac dilatation Any other symptoms are likely to be masked by the severe symptoms from the pulmonary embolism itself the state of shock sudden air hunger oppression in the chest cough weakness and sometimes syncope Substernal oppression due to a complicating angina pectoris or even to a secondary acute myocardial infarction occasionally appears Later symptoms if there is survival for twelve hours or more

may include epigastric discomfort from liver engorgement secondary to heart failure and fever and pleuritic pain due to the pulmonary infarction which is not at first evident

Signs Signs of the acute cor pulmonale include evidence of increase in size of the right ventricle of dilatation of the pulmonary artery and sometimes of failure of the right heart Such signs may be transient or modified because of the coincident occurrence of coronary insufficiency or of vasomotor shock which reduces markedly the return of blood to the right heart and so prevents much dilatation thereof

Characteristic signs related to the pulmonary artery dilatation that have been reported are forceful pulsation of the pulmonary artery evident both by inspection and by palpation along with increased percussion dullness at the left upper border of the heart marked accentuation of the pulmonary second sound a loud blowing pulmonary systolic murmur and a to and fro friction rub over the pulmonary artery very superficial and probably due to the pressure of the bulging artery and infundibulum against the pericardium underlying the sternum

Signs indicative of right ventricular dilatation and failure include increased percussion dullness, diastolic gallop rhythm at the lower end of the sternum and engorgement of the neck veins with or without pulsation There may even be some engorgement of the liver

An interesting and important finding is that of an abnormal electrocardiogram which is characteristic and apparently pathognomonic an *S* wave develops in Lead 1 the *T* wave in Lead 2 tends to be low or inverted a *Q* wave develops in Lead 3 or is increased in amplitude the *T* wave in Lead 3 is quite deeply inverted, and in the precordial leads over the right ventricle in particular V and V_3 but also at times V_4 the *T* waves are flattened or more often inverted (Figure 99) These electrocardiographic changes come and go rather quickly along with changes in the condition of the patient they are for the most part attributable to the acute dilatation of the right ventricle and not so much to anoxemia secondary to the pulmonary embolism itself However they are often masked or replaced in older patients with important degrees of coronary heart disease by patterns of coronary insufficiency or of myocardial infarction

It is important to note that most instances of pulmonary embolism are not attended by the acute cor pulmonale chiefly because the obstruction of the pulmonary circulation is not of high enough degree hence in only a minority of cases of pulmonary embolism should one expect to find the characteristic electrocardiogram It was present in variable degree in 33 out of a series of 92 patients recently studied by the author but well marked in less than half of these making a total of about 10 per cent of the entire series (Murnaghan McGinn and White, 1943) There are therefore normal electrocardiograms in a large percentage of cases of pulmonary embolism although some have abnormal records due to pre-existing heart disease (especially coronary) further affected by the strain of the new vascular accident and in still others there are

suggestions of a slight degree of the acute cor pulmonale with or without underlying heart disease It is of further interest to note as we have found and as has been pointed out by Currens (1942) that myocardial infarction may be precipitated by the strain and anoxemia secondary to pulmonary embolism

Lead

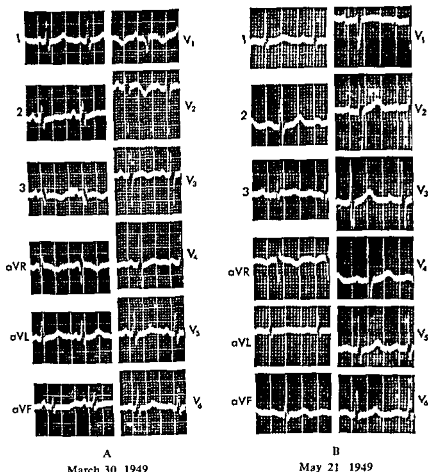


FIG 99 Electrocardiograms in a case of acute cor pulmonale female age 65 (*A*) Bipolar limb leads 1 2 and 3 unipolar limb leads aVR aVL, and aVF and six pre cordial leads V to V inclusive (*B*) Same several weeks after operation with removal of clot from leg vein Time = 0 04 and 0 20 second amplitude 1 mm = 0 10 mv

especially in older persons with less adequate coronary circulations If such an infarct is in the posterior wall the electrocardiographic pattern may be at first confused with that of the acute cor pulmonale or the two may be super imposed as may also be the patterns of anterior myocardial infarction and the acute cor pulmonale Even without actual infarction a temporary state of myocardial anoxia may alter the electrocardiogram but it will not produce

the pattern of the acute cor pulmonale It is always important to explore the precordium electrocardiographically in the second and third positions over lying the right ventricle in the search for abnormality that is flattening or inversion of the *T* waves characteristic of the acute cor pulmonale

Roentgen ray study of the acute cor pulmonale has not yet been adequately carried out in large part because of the very serious and transient nature of the fulminating illness but in rare cases cardiac dilatation has been noted With acute pulmonary embolism the diaphragm on the affected side tends to be elevated but the infarction itself may not be evident for twenty four hours or more and in some cases with good collateral circulation pulmonary em bolism is not followed by infarction

In the acute cor pulmonale the pulse is usually rapid and regular the arterial pressure is low and the venous pressure is often high

Pulmonary embolism either with or without the acute cor pulmonale is often wrongly diagnosed or missed entirely It should always be thought of when there recur at intervals of days to weeks unexplained episodes of chest discomfort dyspnea tachycardia fever or blood spitting Frequently only one of these symptoms is present although as a rule one finds an elevation of temperature pulse rate and respiratory rate together the latter two out of proportion to the height of the fever Pulmonary embolism will be discussed more fully in Chapter 28

Course and prognosis The course and prognosis of the acute cor pulmonale are extremely variable Many cases die quickly more often from the state of shock incidental to the pulmonary embolism than from right heart failure In many cases the condition is probably very transient lasting but a few hours at most and thus accounting for its neglect in the past or confusion with other conditions because of lack of time for study A few cases show the condition for several days prior to recovery or to death from another pulmonary embolus Doubtless in many cases the acute cor pulmonale is but slight and can be recognized only by very careful study

Complications The chief complications of the acute cor pulmonale are vasomotor shock which may abolish the cardiac dilatation recurrent pul monary embolism which is not uncommon and is likely to end fatally myo cardial ischemia or actual infarction particularly in cases with serious coronary artery disease already and congestive heart failure Massive pulmonary em bolism with resulting strain on the right ventricle causing dilatation and failure may itself complicate chronic heart disease and produce a grave condition that not infrequently terminates fatally but the immediate significance of which is often misunderstood this is particularly true of severe mitral stenosis and of hypertensive or coronary heart disease with congestive failure The commonest complication of mitral stenosis and of congestive heart failure is pulmonary embolism and an occasional complication of acute myocardial infarction (from coronary thrombosis) during convalescence is pulmonary embolism which has often been wrongly diagnosed as a new attack of cor onary occlusion

Treatment Therapy of the acute cor pulmonale includes absolute rest with head elevated (unless a state of shock supervenes) morphine ¼ gr (0 015 gm) subcutaneously and oxygen inhalation (by tent) It is advisable to give digitalis in full dosage if the right heart fails digitoxin 0 5 mg intravenously or by mouth repeated in 3 hours and again if necessary or digoxin 0 8 mg intravenously repeated in 3 hours or digitalis leaf in solution 0 5 gm intra venously repeated in 3 hours Pulmonary embolectomy introduced many years ago (Trendelenburg 1908) and carried out in a few cases proved to be an impracticable measure and as a rule unsuccessful because the emboli are so often multiple or split and because the operation itself is so hazardous Papaverine hydrochloride has also been recommended for the treatment of acute cases in the dosage of 0 1 to 0 2 gm but its use is in general disappointing

It is even more important in treatment inasmuch as recovery is likely from the damage already done to search as soon as possible for the thrombosed vein in the leg which has been responsible for the massive pulmonary embolus which in turn has caused the acute cor pulmonale since life hangs in the balance from the threat of another and quite possibly fatal embolus The most careful physical examination may fail to reveal the thrombosed vein contrast (Diodrast) roentgen ray study may show it readily but it is also unreliable and may itself induce thrombosis (see Chapter 28) Ligation of the offending or threatening veins of one or of *both* legs is often necessary to save lives The use of heparin intravenously by constant drip though often helpful is not always adequate and may delay essential surgery

Differential diagnosis The three conditions that are very likely to be con fused with the acute cor pulmonale are (1) acute coronary occlusion with rapid failure of the left ventricle and pulmonary vascular congestion secondary thereto (2) congestive heart failure complicating heart disease and attended by rales at the lung bases which may also result from bilateral pulmonary infarcts (quite commonly occurring at both lung bases and not infrequently concealed behind congestive hydrothorax) and (3) pulmonary infection also attended by rales in the lungs and not uncommonly complicating heart disease A careful history past and present and the electrocardiogram usually dis tinguish these conditions but the greatest difficulty arises when two or all three of them occur simultaneously in the same patient There are two other acute thoracic episodes that although much less common need to be thought of and ruled out when pulmonary embolism is being diagnosed the first namely spontaneous pneumothorax is more frequent and easy to identify the second *spontaneous mediastinal emphysema* a related condition is rare and not always clear it is best diagnosed by the combination of substernal pain a curious crunching sound over the heart in systole roentgen ray evi dence of air in the mediastinum and sometimes an escape of air into the subcutaneous tissues of the neck (Hamman 1939)

COR PULMONALE (PULMONARY HEART DISEASE)

Etiology *Cause* The cause of the condition called chronic pulmonary heart disease is chronically increased resistance in the pulmonary circulation due commonly to the narrowing of its arterioles and capillary bed and not the result of left heart failure mitral stenosis or congenital heart disease The most pronounced and characteristic degree of the chronic cor pulmonale has been that *associated with silicosis extensive pulmonary and pleural fibrosis* and the rare pulmonary endarteritis obliterans In lesser degrees the chronic cor pulmonale may result from marked pulmonary emphysema tracheal or bronchial stenosis pulmonary collapse or, in excessively rare cases in infancy failure of the alveoli to develop chronic inflammatory conditions of lung parenchyma mechanical factors resulting from chest deformities pulmonary arteriovenous communications (fistulae), congenital or acquired and other intrathoracic conditions Infrequently permanent and extensive obstruction of the blood flow in the major pulmonary arterial trunks by large fibrosed thrombi originating as pulmonary emboli from the acute effects of which the patient has recovered is the cause of the chronic cor pulmonale and is likely to be overlooked clinically Rarely pressure on and obstruction of the pulmonary artery by a syphilitic aortic aneurysm (Garvin and Siegel 1939) may be to blame

Primary endarteritis obliterans of the pulmonary arteries noted first in several cases in the nineteenth century is generally of unknown cause but in rare cases it has been ascribed to syphilis (Ayerza 1901 Arrillaga 1912) Because of the deep cyanosis that has been seen in a few cases of this type the patients have been sometimes called black cardiacs but undoubtedly the major part of the cyanosis in these black cardiacs is due to the primary pulmonary disease which prevents the oxygenation of the blood and not to the secondary heart disease although of course, right heart failure with resulting systemic venous stasis accentuates the cyanosis (see Chapter 4) Clinically the effects on the heart of severe chronic pulmonary disease and of pulmonary endarteritis obliterans are much the same and they will be discussed together

Age The heart disease that follows chronic pulmonary lesions occurs mostly in older persons Of the twenty-one cases of White and Jones series all but four were more than 50 years old and thirteen were over 60 years of age in *Scott s series of fifty autopsied cases (Scott and Garvin 1941)* thirty five were over 50 years old and sixteen over 60 The age incidence of primary pulmonary endarteritis is younger the condition being found mostly in young and middle aged men, the youngest case that I have encountered was a boy 11 years old at death

Sex With respect to the cor pulmonale males are much in the majority as might be expected in view of their well known greater incidence of marked emphysema and pneumoconiosis (silicosis anthracosis asbestosis) Of 25 cases of chronic cor pulmonale of high degree found among 4 000 autopsies

at the Massachusetts General Hospital in the ten year period of 1932 to 1942 20 were male and only 5 were female (White personal analysis in 1942) in Scott s series of 50 cases, 48 were male and only 2 were female

Predisposing factors Severe climate poverty malnutrition and hereditary influences are factors which favor the occurrence of chronic pulmonary disease and thoracic deformities responsible for the chronic cor pulmonale but one of the most common predisposing factors of all is pneumoconiosis (especially anthracosis and silicosis) an industrial disease among coal miners and stone workers The coal or stone dust may saturate the lungs in a very few years to cause marked fibrosis and obliteration of many small arteries in the lungs tuberculosis and pneumonia are the common causes of death in these cases but a few succumb to heart failure, with improvement in industrial hygiene this hazard is lessening

Pathology The chronic cor pulmonale or pulmonary heart disease consists primarily of enlargement of the right ventricle (Figure 100 page 508) and of the pulmonary artery and secondarily of enlargement of the right atrium The increase in size of the right ventricle is due at first to hypertrophy as in the case of the left ventricular enlargement in systemic hypertension later as the heart fails dilatation of the right ventricle appears with relative tricuspid insufficiency and right atrial dilatation The essential lesion is that of hyper trophy of the individual muscle cells of the right ventricle Such changes as fibrosis fatty degeneration and fatty infiltration are associated with certain other conditions namely coronary disease anemia and obesity Failure when it comes is attended by dilatation due to muscular fatigue and not to de generative changes unless there are complications Endocarditis and peri carditis occur only as rare and incidental complications in pulmonary heart disease

The right ventricle may be but slightly hypertrophied in the milder cases adding but little to the heart weight escaping clinical observation and passing notice sometimes even at postmortem examination Usually the enlargement is considerable and in rare cases it may be very great so that the right ventricle is as large as or larger than the left ventricle and the blunt apex of the heart is made up in large part by the right ventricle (see Figure 101 as an example of marked right ventricular enlargement)

The pulmonary artery and its branches may show areas of atheroma of varying number and size and some narrowing of the smaller arteries when the blood pressure in the pulmonary circulation is much elevated which happens in some cases of chronic pulmonary disease as it does in chronic mitral stenosis There is a different finding however in the case of pulmonary endarteritis obliterans the rarer pulmonary cause of the chronic cor pul monale here one finds an actual hyperplasia of varying degree of the endothe lium of the smaller arteries and arterioles in extreme cases almost a complete arterial obliteration In a few cases the treponemata of syphilis are reported to have been found in these endothelial lesions in most cases the cause is still unknown The left ventricle in the case of chronic pulmonary disease is not

primarily affected It may, however, as in mitral stenosis be rather smaller than usual this finding has probably given rise to the erroneous idea that chronic pulmonary disease and emphysema always spare the heart and result in cardiac hypoplasia

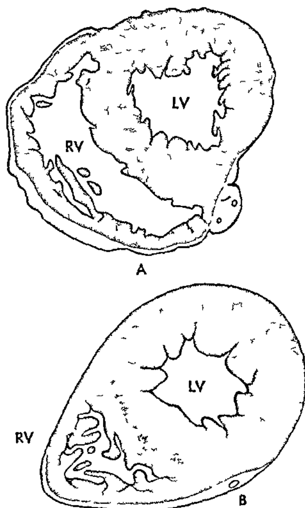


FIG 100 Drawings showing cross sections of (*A*) a dilated cor pulmonale and of (*B*) a normal heart at a level two thirds of the distance from base to apex of the ventricles These cross sections are of natural size RV = right ventricle LV = left ventricle

In the case of silicosis two morphologic processes have been described which evoke vascular changes in the pulmonary circulation (1) direct encroachment on the vascular wall by nodules or nodular masses and (2) infiltration of the vascular wall by dust bearing and pigment bearing granulation tissue (Geever 1947)

A very rare bizarre finding as a cause of the chronic cor pulmonale in infancy is failure of the lung alveoli normally to open up at birth this results in

an extremely difficult bronchiolar respiration endarteritis marked enlargement of the right ventricle and early death within the first year (T B Mallory personal communication 1942) A rare cause of subacute cor pulmonale is a gradual vascular obliteration by carcinomatous emboli (Mason 1940)

Symptoms The chronic cor pulmonale produces symptoms only when it begins to fail Symptoms due to the chronic underlying pulmonary disease namely dyspnea cough and weakness have often been wrongly interpreted as those of early failure in pulmonary heart disease this error was made in the first edition of this book Actually symptoms of the heart failure are other than pulmonary and are due to congestion of liver gastrointestinal tract and dependent parts of the body Pain except in the congested liver, and palpitation are rare and not characteristic

Signs There may be little or no evidence of the chronic cor pulmonale itself because it so often is concealed by the underlying pulmonary condition but when the characteristic signs of marked chronic pulmonary fibrosis with emphysema are present one may rest assured that the heart is at least somewhat affected although it may still be competent A brief summary will first be given of the typical signs of advanced pulmonary fibrosis with emphysema and then the additional signs of cardiac involvement due to that condition

The signs of marked pulmonary fibrosis with emphysema are (1) cyanosis of varying degree often considerable and sometimes as intense as in the maladie bleue of congenital heart disease (2) clubbing of the fingers and toes (3) polycythemia the red blood cells being increased to 6 or 7 millions per cubic millimeter (4) lowered oxygen saturation of the arterial blood (5) restricted respiratory movements with emphysematous or asthmatic breathing (expiration prolonged and forceful) (6) frequent scattered squeaking or groaning pulmonary rales (7) low position of diaphragm with restricted respiratory movements very evident fluoroscopically (8) abnormally thickset or barrel shaped chest and (9) low vital capacity Most of these signs are also found in the cyanotic type of congenital heart disease and also except for the constant cyanosis and rales in long time residents at very high altitudes (over 12 000 feet or 4 000 meters)

The cardiac signs are those due to enlargement of the right ventricle and to a complicating failure when it appears Cardiac arrhythmia is uncommonly found There is frequently a pulmonary systolic murmur and the pulmonary second sound is usually accentuated The pulmonary arterial pressure is elevated to double or more the normal pressure (e g 50 or 60 mm mercury instead of 25) when tested by intracardiac catheterization The systemic blood pressure is as a rule low at about 100 to 110 mm systolic and 70 to 80 mm diastolic

The signs of failure are primarily those of failure of the right ventricle consisting of engorgement of the great veins including the jugular veins with the development of a jugular venous pulse in the upright and semiupright posture liver enlargement and tenderness ascites and edema of the legs Pulmonary signs are wholly those of the underlying pulmonary disease

The right ventricular enlargement is often made out with much difficulty especially on physical examination There are three reasons for this difficulty in the first place, the right ventricle being anteriorly placed shows relatively less evidence of enlargement than does the left ventricle which increases downward and to the left as well as backward, secondly the low level of the diaphragm so often found in chronic pulmonary disease gives a deceptive small cardiac appearance (a drop heart) even when the heart is somewhat enlarged and thirdly the pulmonary emphysema, by making the thorax hyperresonant often prevents satisfactory percussion for the determination of the heart borders and even interferes with auscultation Thus unless great care is exerted and electrocardiograph and roentgen ray are brought to one's assistance the enlargement of the chronic cor pulmonale may easily escape notice even with all this help the condition may be discovered only at post mortem examination Electrocardiography shows right ventricular preponderance (Figure 101) unless there is also present left ventricular enlargement from some factor of strain (systemic hypertension aortic valve disease or myocardial infarction) in the same heart The right ventricular preponderance pattern includes abnormal right axis deviation in the limb leads and especially higher peaks of the *R* waves in the precordial leads over the right ventricle (often with depressed or inverted *T* waves) and prominent *S* waves over the left ventricle Roentgen ray study may or may not clearly show the right ventricular enlargement (Figure 102 see page 512), the view of the heart shadow in the anterior oblique positions is especially helpful in revealing the forward bulging of the right ventricle not made out in the anteroposterior position Furthermore fluoroscopy sometimes shows dynamic dilatation of the pulmonary artery which may be marked especially in the case of pulmonary endarteritis obliterans In this last named condition the lung fields have been noted as abnormally clear but as a rule the lung fields are very abnormal due to the underlying pulmonary disease silicosis, or chest deformity

Course and prognosis Pulmonary heart disease or the chronic cor pulmonale begins very gradually and insidiously usually in the long course of severe chronic bronchitis and emphysema or silicosis and years may elapse after it has been found before failure becomes marked Its course and prognosis are so bound up with those of the pulmonary condition that the heart trouble must always be considered with the lung disease Pulmonary infections especially pneumonia and phthisis have in the past usually caused death in these cases but many years of a careful life of moderate activity may elapse before death comes It is probable that the limitations enforced by the pulmonary trouble protect the heart from excessive fatigue Death from congestive heart failure in such patients occurs rarely

The prognosis of cases with pulmonary endarteritis obliterans is less favorable than that of cases with chronic pulmonary fibrosis death coming from cardiac failure in the course of months to a few years at best after cyanosis has become apparent

Complications The two important complications heart failure either right

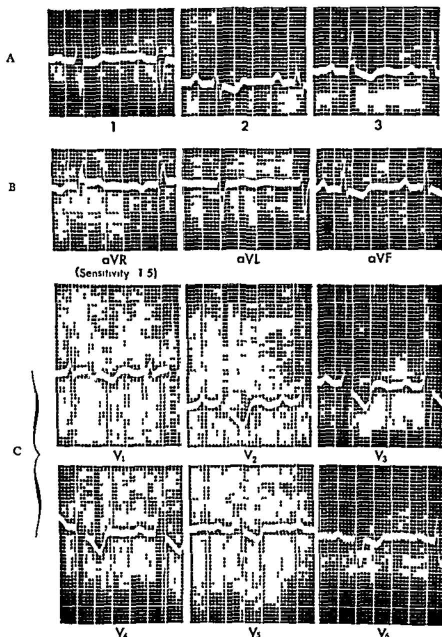


FIG 101 Electrocardiogram in a case of chronic cor pulmonale male age 30 (*A*) Bipolar limb leads 1 2 and 3 (*B*) unipolar limb leads aVR aVL, and aVF (*C*) six precordial leads V_1 to V inclusive Note the marked right axis deviation in the limb leads and the very high *R* and inverted *T* waves in the precordial leads V to V over the right ventricle Time — 0 04 and 0 20 second amplitude 1 5 mm = 0 15 mv

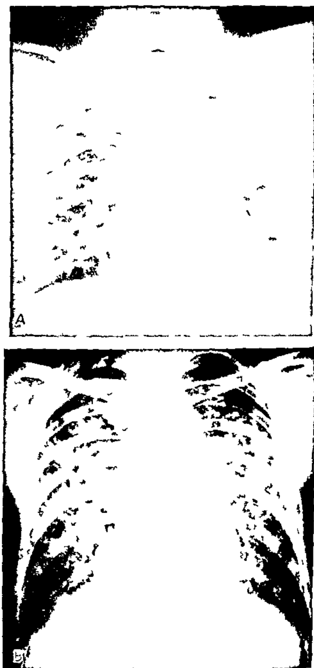


FIG 10. Roentgenograms in two cases of the chronic cor pulmonale due to pulmonary endarteritis obliterans and pulmonary fibrosis (*A*) Roentgenogram showing increased heart (right ventricular) size and prominence of pulmonary artery Boy age 10 who showed at autopsy a year later very extensive pulmonary endarteritis obliterans of unknown cause (*B*) Roentgenogram showing extensive pulmonary fibrosis and chronic cor pulmonale in H S G male age 49

aid d or incidentally left sided and respiratory infections have been discussed above Other types of heart disease may be associated with the chronic cor pulmonale but only one coronary heart disease occurs with much frequency Coronary heart disease is present in about half the cases probably because of the advanced age of the majority of the patients

Treatment The treatment of pulmonary heart disease consists in the therapy both of heart failure when present and of the pulmonary disease itself but much more so of the latter since heart failure is rare in these patients The usual therapy of congestive failure if clearly present as shown by engorged liver leg edema and increased jugular pulse should be carried out (but not for dyspnea or cyanosis per se) rest in bed digitalis diuretics and symptomatic treatment as needed Oxygen inhalation may prove to be especially helpful because of the pulmonary disease

A therapeutic test with digitalis in cases of chronic bronchitis and emphysema is often helpful since heart weakness is easily masked by the pulmonary condition When signs of right heart weakness are thereby decreased we have confirmatory evidence of the chronic cor pulmonale or of a secondary effect of coincidental left heart weakness careful differentiation between these two fundamental conditions is essential and will be discussed at length in Part IV When however dyspnea cough and cyanosis are appreciably decreased by saturation of the patient with digitalis we have evidence only of left ventricular weakness and failure and not of the chronic cor pulmonale If in either case there has been benefit by digitalis its administration should thereafter constantly be maintained by daily rations of the drug and in cases of considerable right ventricular enlargement it is conceivable that regular rations of digitalis may help to retard the onset of heart failure in the first place

Care to avoid respiratory infections the treatment of the pulmonary condition already present the avoidance of fatigue residence in a more favorable (drier) climate and not at high altitudes and symptomatic therapy especially the use of penicillin and oxygen as needed will have a favorable influence on the course of pulmonary heart disease

If syphilis is found present in rare cases of pulmonary endarteritis obliterans specific therapy should be instituted with care as outlined for syphilitic aortitis in Chapter 16

Advances in thoracic surgery in the correction of chest deformities and pulmonary disease afford some hope for the future eradication of underlying causes of the chronic cor pulmonale in a few cases even perhaps the removal of extensive thrombi more or less organized from the pulmonary artery itself or from its chief branches in rare subacute or chronic cases when the responsible factor is obviously embolic thrombosis

Differential diagnosis There are two conditions from which it is often difficult to distinguish pulmonary heart disease (1) the pulmonary disease itself and (2) congenital heart disease without characteristic murmurs (as in some cases of the tetralogy of Fallot, which consists of pulmonary stenosis

interventricular septal defect, dextroposition of the aorta and enlarged right ventricle) The presence of the emphysema the absence of any history of heart trouble or cyanosis in youth and the lesser degree of abnormality of the heart as determined by various methods of examination help to distinguish the chronic cor pulmonale from congenital heart disease though it is to be noted that pulmonary arteriolar disease and emphysema may themselves be important complications of congenital heart disease (the maladie bleue) The finding of right ventricular enlargement by roentgen ray and electrocardiogram the favorable response to the therapeutic test with digitalis and indeed the very presence of marked chronic emphysema point to pulmonary heart disease as a complication of emphysema Pulmonary endarteritis obliterans is found in younger individuals without pulmonary disease itself is sometimes attended by intense cyanosis (the black cardiacs) and has usually a rapid downhill course Mitral stenosis may in rare cases simulate pulmonary heart disease when the pulmonary vascular congestion is considerable and the right heart begins to fail but careful study, particularly the finding of the characteristic mitral diastolic murmur should clearly distinguish the two conditions

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CHAPTER 21

CORONARY HEART DISEASE
ANGINA PECTORIS
CORONARY THROMBOSIS AND MYOCARDIAL INFARCTION

Introduction For convenience and consistency a simple rearrangement has been introduced into this new edition whereby the former Chapter 31 on Coronary Insufficiency Including the Symptom Angina Pectoris has been for the most part incorporated into the present chapter where it best belongs [1] thus omitting considerable repetition and saving space and the short appendix on Atherosclerosis has been transferred appropriately to Chapters 26 and 28

This chapter is *one of the most important in the book and demands at the* outset the consideration of basic definitions nomenclature and arrangement too often neglected or confused in the rapidly growing literature on the subject In the first place coronary disease is not heart disease though it is often loosely and inaccurately designated as such Strictly it does not even mean coronary artery disease since coronary veins form an important part of the coronary circulation common usage however and the fact that in the present state of our knowledge the coronary veins are not the site of any serious pathologic process justify the use of the term as synonymous with coronary arterial disease Also since practically the totality of coronary arterial disease is atherosclerotic in type coronary atherosclerosis is implied when the term coronary disease is used without other qualification The designations coronary insufficiency and coronary failure usually attended by the symptom angina pectoris and often leading to myocardial infarction are not strictly synonymous with coronary disease since other conditions such as syphilitic aortitis with a blocking of the coronary circulation at its origin may be the cause and since *coronary disease* even extensive in degree may be present without insufficiency of blood supply to the heart muscle

The terms coronary occlusion and coronary thrombosis have been loosely used to indicate myocardial infarction but there should be a correction

[1] I am grateful to Sir John Parkinson for his helpful advice in this respect.

of this common error To be sure myocardial infarction often results from acute coronary thrombosis or occlusion but the two designations should not be employed synonymously myocardial infarction may occur without actual complete coronary arterial thrombosis or occlusion and coronary occlusion may occur without myocardial infarction, if the process is slow in development or (and) the collateral circulation is adequate What has usually been meant clinically by the diagnosis of coronary thrombosis as an acute illness is myocardial infarction The terms coronary occlusion and coronary thrombosis are not strictly synonymous either although as acute processes they can be so considered for practical purposes, old calcareous occlusions of the coronary arteries may exist with never any symptoms therefrom and not even proof of past thrombosis

Finally the term coronary heart disease continues to be to my mind the best designation for the various effects of coronary arterial disease on the heart deleterious enough to cause symptoms or signs or postmortem evidence of more than trivial damage to the heart itself chiefly of course to the heart muscle Thus myocardial ischemia with angina pectoris or electrocardiographic abnormalities due to coronary disease acute myocardial infarction and old scars of similar origin are all included under this heading In the first two editions of this book acute coronary thrombosis with myocardial infarction was not considered as was the general custom in those days as a separate entity in a chapter by itself since it is but a phase of coronary heart disease New knowledge has confirmed the soundness of continuing this procedure in the third and fourth editions

Historical The earliest correlation of coronary disease with serious illness was made by Bonetus in 1700 in the second edition of his *Sepulchretum* when he described the case of a fat middle aged poet who succumbed in a few minutes after the onset of distress in breathing (which may have been angina pectoris) and who showed at autopsy calcified coronary vessels which were almost if not completely occluded Morgagni in 1761 was however unaware of the symptomatology of coronary disease and seven years later (1768) Heberden (quoted on page 538 of this chapter) was unaware that angina pectoris which he described so well was due to heart trouble It was Jenner a few years later (in 1772 as quoted by Parry 1799) who made that discovery Fothergill (1776) and Black (1794) published case reports of angina pectoris with ossified coronary arteries and the former also described myocardial scars

During the nineteenth century and until our own generation (Herrick 1912) astonishingly little advance was made in the clinical recognition of coronary heart disease despite the important contributions mostly anatomic of Weigert (1880) Cohnheim (1881) Ziegler (1881) Huber (1882) Leyden (1884) and Marie (1896)

The following quotation from Herrick s classical paper presents the earliest complete clinical description of sudden coronary occlusion Herrick recog

nized even at the beginning that the clinical picture is often complex and variable a fact that has been re emphasized of late

Herrick J B Clinical Features of Sudden Obstruction of the Coronary Arteries *J A M A* 1912 LIX 2015

Obstruction of a coronary artery or of any of its large branches has long been regarded as a serious accident Several events contributed toward the prevalence of the view that this condition was almost always suddenly fatal

But there are reasons for believing that even large branches of the coronary arteries may be occluded—at time acutely occluded—without resulting death at least without death in the immediate future Even the main trunk may at times be obstructed and the patient live It is the object of this paper to present a few facts along this line and particularly to describe some of the clinical manifestations of sudden yet not immediately fatal cases of coronary obstruction

The influence of the vessels of Thebesius is also not to be overlooked in this connection compensatory circulation through these accessory channels may be of considerable importance in nourishing areas of heart muscle poorly supplied by sclerotic or obstructed arteries

The clinical manifestations of coronary obstruction will evidently vary greatly depending on the size location and number of vesse s occluded No simple picture of the condition can therefore be drawn All attempts at dividing these clinical manifestations into groups must be artificial and more or less imperfect Yet such an attempt is not without value as it enables one the better to understand the gravity of an obstructive accident to differentiate it from other conditions presenting somewhat similar symptoms and to employ a more rational therapy that may to a slight extent at least be more efficient

A study of cases of this type shows that nearly all are in men past the middle period of life Previous attacks of angina have generally been experienced though as shown by my first case the fatal thrombosis may bring on the first seizure The seizure is described by patients who have had previous experience with angina as of unusual severity and the pain persists much longer In some instances there has been no definite radiation of the pain as to the neck or left arm though this may have been a feature of other anginal attacks and the pain as in these two cases may be referred to the lower sternal region or definitely to the upper abdomen Cases with little or no pain have been described Nausea and vomiting with belching of gas are common There may be tympany *Ashy countenance* cold sweat, and feeble pulse complete the picture of collapse The attention of the patient and the physician as well may therefore be strongly focussed on the abdomen and some serious abdominal accident be regarded as the cause of the sudden pain nausea collapse

Cohnheim found that in dogs the pulse after obstruction was slow This may be seen in the thrombotic obstruction of disease in man In Hammer s case (1878) the pulse dropped from 80 to 8 per minute the patient living thirty hours from the onset of the symptoms that marked the closure of the right coronary opening A rapid pulse is frequently seen however The pulse may be irregular A striking feature has been its weakness Blood pressure is low The heart tones have been feeble—in fact often startlingly feeble

Dyspnea and cyanosis have been variable at times much less than one would expect from the character of the accident and the quality of the heart s action Rales dry and moist have been present in many cases

General weakness has been marked in some cases in others not

The occurrence of serofibrinous exudate over the area of myocardial softening with roughening of the pericardium has been noted in several instances This may explain a later precordial distress as in Case 1 A fine pericardial friction there fore occurring several hours or a few days after the initial pain may be confirma tory evidence of coronary obstruction

Death may be caused by rupture by sudden asystole or by gradual giving out of the weakened heart muscle

Emphasis ought to be laid on the resemblance of some of these cases to sur gical accidents

If these cases are recognized the importance of absolute rest in bed for several days is clear It would also seem to be far wiser to use digitalis strophanthus or their congeners than to follow the routine practice of giving nitroglycerine or allied drugs

Incidence Extensive coronary arteriosclerosis is not only a very frequent and important cause of heart trouble near the end of the life cycle but it also cripples and kills often in the prime of life and sometimes even in youth It is problematic whether the coronary sclerosis of senile life can ever be con trolled but it is to be hoped and expected that some progress can be made in the prevention of such disease in persons who have not reached old age

Coronary atheroma and sclerosis of slight to moderate degree are doubtless but part and parcel of the process of growing old Not only is it difficult in deed impossible in the present stage of our knowledge to recognize the limits of the normal range anatomically as well as clinically at any particular age but even when the coronary arteries are markedly involved the heart itself may remain both structurally and functionally essentially normal This is a very important but inadequately recognized fact Of a series of 1 000 con secutive postmortem examinations 371 cases (37 1 per cent) showed macro scopic coronary disease while of these 371 cases only 238 (64 per cent) showed any definite myocardial lesions (fatty change alone in 48 of them and fibrosis in the remaining 190) (Allan 1928) It is furthermore to be ob served that limitation of blood supply to the heart by narrowed coronary vessels may limit cardiac action and reserve without actually causing structural lesions.

Coronary sclerosis as a cause of heart disease varies somewhat in its relative incidence in different parts of the world largely according to the frequency of such other causes as rheumatic heart disease hypertension and syphilitic aortitis It is of interest that although heart disease has been on the increase since 1930 this has largely been due to a rise in the incidence of coronary heart disease in contrast to other types of heart disease (Figure 103) In New England 37 per cent of a series of 2 314 patients with organic heart disease were diagnosed as having some grade of coronary heart disease in about half of them uncomplicated and in the other half complicating other types of

heart disease mostly the hypertensive type (White and Jones 1928) A recent survey of 3 000 cardiac patients in New England showed a considerable increase of the relative incidence of coronary heart disease up to 48 5 per cent (White 1951)

In Clawson s series (1941) of 4 678 cardiac deaths among 30 265 autopsies there were 1 215 cases of coronary heart disease (30 per cent of the cardiac cases) three quarters of which were also hypertensive Statistics at present are not truly comparable for sometimes only those cases are recorded as

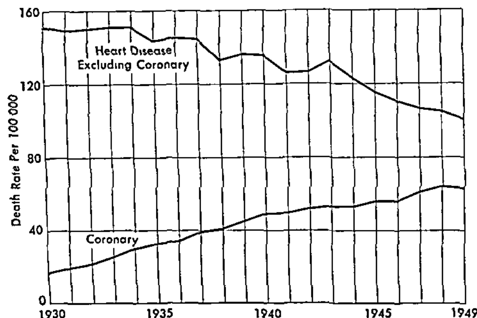


FIG 103 Annual age adjusted death rates of insured individuals from diseases of the coronary arteries as compared with other chronic diseases of the heart Ages 1 to 74 years Metropolitan Life Insurance Company 1930–1949 (*Statistical Bulletin* Metropolitan Life Insurance Company New York City [January] 1950 XXXI 11)

coronary heart disease in which the coronary involvement is the primary cause of disability or death while sometimes all cases are so tabulated that show any suggestion of coronary involvement whatsoever We need many more studies than we possess at present to determine to what extent coronary disease including coronary thrombosis has been increasing if at all in the present generation Two representative studies of the few that are available are as follows Meakins and Eakin (1932) found that the percentage of incidence of coronary thrombosis with occlusion (slightly less than 1 per cent) among the autopsies at the Royal Victoria Hospital in Montreal in the five year period from 1926 to 1930 inclusive was actually less than that from 1896 to 1900 inclusive and Levy Bruenn and Kurtz (1934) reported that the autopsy diagnosis of coronary disease at the Presbyterian Hospital in New York City

increased from 17 8 per cent in the decade from 1910 to 1920 to but 30 4 per cent in the next decade while the cases with the clinical diagnosis of coronary disease jumped from 7 to 454 The autopsy diagnosis of coronary thrombosis and of myocardial infarction at the Massachusetts General Hospital rose rapidly in incidence among the total autopsies from rare cases in the middle 1920 s to 13 to 14 per cent in 1940 and 1941 probably due in considerable part to more careful search by the pathologists (Wang et al 1948) It may be that coronary heart disease or its symptoms, in particular angina pectoris are more common in this day and age, at any rate it is certain that the diagnosis is much more often made during life Even young people with coronary heart disease are now being reported quite often the largest series being 866 in number 450 of whom were confirmed at autopsy aged 18 to 39 years in U S A military service (Yater et al 1948)

Etiology *Cause* The reduction of the blood supply to the myocardium explains the deleterious effect of coronary disease on the heart This blood supply is reduced by the narrowing or obstruction of the coronary arteries locally or generally a slight degree of abnormality of the coronary arteries may exist however without restriction of blood flow Moreover other causes exist for a poor blood supply to the myocardium even when the coronary arteries themselves are normal severe anemia marked aortic stenosis or regurgitation extreme bradycardia extreme tachycardia marked temporary hypotension (as with vasodilatation in surgical shock) and blocking of the mouths of the coronary arteries by large vegetations on the aortic valve or by syphilitic aortitis

Coronary disease may be of various types In the normal evolution of the coronary circulation simple thickening of the elastic hyperplastic layer of the intima may occur so that in contrast to other arteries of the same size the intima may exceed the media in thickness doubtless due to the fact that these are the smallest vessels receiving blood under a high head of pressure (Wolkoff 1929) only if this change is marked is it to be considered as pathologic A fibrotic thickening may also develop especially in certain areas Dock (1946) reported the findings of a thicker coronary wall and relatively narrower lumen normally in the male than in the female infant

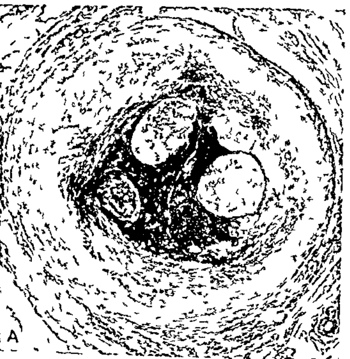
In the great majority of cases of coronary artery disease ordinary *atheroma* (*αθηρη* meal or porridge) is to blame this consists of softening the precursor of arteriosclerosis with yellowish fatty (cholesterol) areas in the endarterium Fibrosis, thickening so-called cholesterol abscesses and calcification ensue and the arteries may become brittle, the abscesses sometimes break or give rise to ulcerations whereby thrombi may form Hemorrhages from the rupture of minute vessels (vasa vasorum) in the vascularized atherosclerotic walls of the diseased coronary arteries are thought also to favor or to precipitate coronary thrombosis (Paterson 1936 1941) A tendency to either thrombosis on the one hand or to hemorrhage on the other as characteristic of cases of acute coronary occlusion has been suggested in the past but not confirmed Reaction to atheroma is both fibrosis and especially in older decades calcifi

cation and the formation of cholesterol abscesses (Leary 1935) See Figures 104 and 105

The cause of atheroma of the coronary arteries, as well as that of arterio sclerosis in general is still unknown Faulty cholesterol metabolism, local



FIG 104 Microphotographs of coronary arteries with moderate atherosclerosis (*A*) High power magnification of lipoid cells underlying the endothelium and overlying collagenous bands of fibrous tissue (scarring from previous deposits of the sort) in a coronary artery of a man of 54 years X 280 (*B*) Microphotograph of coronary arteries in a youthful case of extensive coronary atherosclerosis X 30 times Man age 26 collapsed while removing a wheel from an automobile and died in a few minutes Note the almost complete obstruction of the descending branch of the left coronary artery by the extensive intimal fibrosis with necrosis in the deepest layer (crescentic in shape) just overlying the media and the blocking of the small remaining lumen by a fresh antemortem clot (stained black and roughly U-shaped) (Kindness of Dr Timothy Leary Bo ton City Hospital Boston)



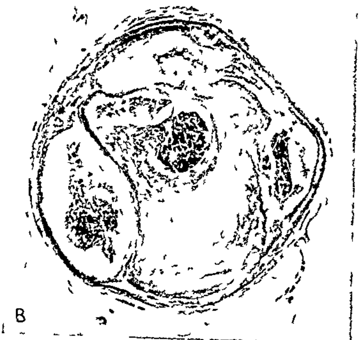


FIG 105 Microphotographs of cross sections of coronary arteries in two cases of extensive coronary atherosclerosis showing later developments X 30 times (*A*) Man age 53 who died suddenly at a railroad station he had had no illness and had worked continuously Note almost complete obliteration of anterior descending branch of the left coronary artery with recanalization of an organizing thrombus in the old lumen There is one new artery at the left and three veins above and to the right (*B*) Man age 62 found dead the day after strenuous work Note the markedly fibrosed lumen of the anterior descending branch of the left coronary artery with four so-called "atheromatous abscesses (atherocheumata) one discharging into the mall oval lumen of the artery in which there is a fresh antemortem thrombus (Kindness of Dr Timothy Leary Boston City Hosp tal Boston)

arterial strain or overwork hypertension infection allergy endocrinopathy and heredity are among the many factors suggested but none has been proved or even consistently found The frequent finding of a high blood cholesterol content in fasting cases of coronary heart disease especially in the young patients under 40 along with a low basal metabolic rate is in favor of a disturbance of fat metabolism at least as one factor The suggestion of local overwork or strain is supported in the case of coronary atheroma by the finding that it is most common at the bend of the descending branch of the left coronary artery just below its mouth and that serious coronary sclerosis relatively is more common in hypertensive individuals than in persons with normal blood pressure the hypertension antedating any evidence of coronary disease the frequency of coronary disease in myxedema and diabetes supports the idea of a factor of disturbed fat metabolism secondary to endocrinopathy and the factor of heredity is supported by the frequent finding of several members of a single family with serious coronary sclerosis The combination of several etiologic factors is plausible

An interesting presentation by Moreton (1948) of a possible mechanism based on the physiochemical introduction of coarse particulate matter containing fat (large lipid molecules) into the coronary artery wall where it acts as a foreign body illustrates a current viewpoint

Considerable research is now in progress in an attempt to determine the responsibility of blood cholesterol and other lipids in the genesis of serious coronary atherosclerosis Three varied types of investigation may be cited as examples of such research

1 *Chemical* An investigation of 100 persons (97 males and 3 females) who had acute coronary occlusion before the age of 40 years (Gertler and Garn and associates 1950) have shown that more significant than the total cholesterol content of the blood which was found to be elevated in most cases was the ratio of such cholesterol to other phospholipids this was considerably higher than normal Incidentally the blood uric acid was also found to be on the high side and this figure added to the other two in the form of a quotient has proved of considerable interest

In keeping with this chemical study Barr (1951) has found in another chemical study of the blood fractions in atherosclerotic cases a higher ratio than normal of *beta* lipoprotein which contains a larger amount of cholesterol in relation to phospholipids to *alpha* lipoprotein which contains much less cholesterol in relation to phospholipids

2 *Physical* Research on the blood lipoproteins by the use of the ultracentrifuge has also proved to be of special interest Gofman et al (1950) found appreciably more of a light molecule of cholesterol protein floated at a so-called SF 10 to 20 level in patients after recovery from acute myocardial infarction than in the case of normal controls for example 95 per cent in males and 100 per cent in females as compared to 60 and 45 per cent re spectively at the age of 40 to 50 years

3 *Tissue culture* Finally Simms (1948) has tested the amount of lip-

fanogens (precursors of visible fat) and of an inhibiting enzyme called anti lipfanogen in the blood of normal and diseased individuals by determining the amount of fat taken up from the blood by tissue cultures He has found that the ratio of antilipfanogen to lipfanogen, which is 1 0 in normal individuals is much reduced in cases of nephrosis and diabetes and moderately reduced in patients with coronary heart disease

A comparison of the findings of these three different technics chemical physical and by tissue culture is in progress

It is of interest to point out that the foods which contain maximum amounts of cholesterol in order of content per average serving (not per weight) are brains, liver sweetbread scallops oysters eggs, lobster crabs beef veal pork cheese etc By weight, eggs are second after brain

On the other hand it is also current opinion that the cholesterol that is deposited in the coronary artery wall may be produced in large part within the body itself, that is that it may be of endogenous origin It conceivably may be both It seems very likely that the total caloric value of the diet may be more important than the food elements themselves inasmuch as cholesterol may quite possibly be produced richly on a solely carbohydrate diet if hearty enough (witness the cow) if an inadequate or barely adequate diet (in calories) is given it is not so likely that cholesterol in large amount will be deposited in the coronary arterial intima whatever the food ingested may consist of but that an excess diet with gain in weight may have such an effect more readily (?) if there is rich cholesterol intake Here however we are dealing only with conjectures

A different and rare type of coronary disease is that due to syphilis here the media is primarily involved but later the intima too

Still another type of coronary disease and one that is relatively infrequent is that due to *rheumatic* or *other nonsyphilitic infection* The intima and media are involved and there may even result aneurysmal dilatation (mycotic aneurysms)

Endarteritis obliterans is a very rare cause of coronary artery disease it is *most often only a complication being found in other* vessels than the coronaries mostly in the legs It is itself of unknown origin but the excessive use of tobacco has been suggested as an etiologic factor Related to this and of obscure origin is an extensive disease of the whole coronary artery wall in infants (Stryker 1946 Menten and Fetterman 1948) *Periarteritis nodosa* may involve the coronary arteries at any age and has been noted to cause coronary thrombosis and myocardial infarction at even the early age of 1 year (Pickard et al 1947)

The coronary arteries healthy or relatively healthy themselves may rarely be blocked by *emboli* even of air so that death or cardiac infarction may result or they may be more or less occluded at their mouths by syphilitic aortitis or by aortic valve vegetations in bacterial endocarditis The pressure of tumors and perhaps even of pericardial fluid and constricting adhesions may interfere with the coronary *blood flow*

Trauma of the coronary arteries has been infrequently encountered as the result of pericardial paracentesis stab and gunshot wounds and unusual accidents Hemopericardium and death from tamponade generally follow such trauma

Rupture of a coronary artery may not only follow trauma but is a rare spontaneous occurrence as the result of a *dissecting aneurysm* extending from the aorta or limited to the coronary artery itself as a sequel to coronary thrombosis Coronary aneurysms themselves are rare they may be congenital mycotic embolic syphilitic or arteriosclerotic—a series of 47 cases collected from the literature (Scott 1948) showed 15 of the first 12 of the second 6 of the third 6 of the fourth while the remaining 8 were miscellaneous or unclassified

Finally *congenital abnormalities* of the coronary arteries may very rarely account for trouble when the cardiac activity is such that a single vessel or some other restriction of blood supply is incapable of maintaining a normal blood flow to the myocardium or when one of the coronary arteries arises from the pulmonary artery with resulting myocardial necrosis in the part of the heart supplied by this vessel Such an anomaly the left coronary artery coming off the pulmonary artery was responsible for left ventricular myocardial necrosis enlargement and failure and for attacks of distress on effort which were probably angina pectoris followed by early death in a four months old infant (Bland White and Garland 1933) Coronary arteriovenous aneurysms or fistulae occur very rarely I have encountered one such case in a boy of 9 years without disability who showed a continuous murmur at the right of the lower end of the sternum arousing a suspicion of coronary involvement which was found on surgical exploration (Paul Sweet and White 1949)

Age The age of occurrence of coronary disease and accordingly of myocardial changes due to coronary disease varies from youth to extreme old age, but it naturally increases with years Statistical studies of the age incidence of coronary disease are likely to be misleading because of the fact that slight atheromatous or atherosclerotic changes are frequently found in the coronary arteries on routine postmortem examination without their having any clinical importance whatsoever and hence not actually constituting disease from the clinical point of view and because a good many old persons with slight coronary insufficiency due to coronary disease do not trouble to seek medical advice since they consider their condition to be simply a part of old age as in fact it is Several studies in particular those by Wolkoff (1929) by Ehrich and his associates (1931) and by Leary (1935) have shown that atheromatous changes may be seen in the coronary arteries as early as the first decade when they may still be retrogressive Atheroma and increase in thickness of the elastic hyperplastic layer of the intima are found frequently in the anterior descending branch of the left coronary artery in the second decade and regularly in all cases over forty years of age such changes are found later by about two decades in the right coronary artery and other large branches The age groups of 864 cases of coronary heart disease diagnosed clinically

in New England (White and Jones 1928) as compared with 1 346 recent cases (White 1951) have been reported as follows

Table 9

AGE GROUPING OF CASES OF CORONARY HEART DISEASE

		Group of 864 Cases Reported in 1928 Percentage		Group of 1,346 Cases Reported in 1951 Percentage	
Clinical coronary heart disease	Under 40 years of age	0 2		3 8	
	40 to 50 years of age	6 1		12 3	
	50 to 60 years of age	22 7	93 7	26 5	83 9
	60 to 70 years of age	44 1		33 1	
	Over 70 years of age	26 9		24 3	

This age grouping represents a cross section of the cases as they were seen by us *the ages at onset of the disease would average a few years earlier* as noted below

A series of 497 cases of angina pectoris gave the following age grouping at the onset of their disease (White Bland and Miskall 1943)

Angina pectoris (age at onset)	30 years of age and under	4 cases	0 8 per cent
	31 to 40 years of age	16 cases	3 2 per cent
	41 to 50 years of age	106 cases	21 4 per cent
	51 to 60 years of age	206 cases	41 4 per cent
	61 to 70 years of age	131 cases	26 4 per cent
	71 to 80 years of age	34 cases	6 8 per cent
	Over 80 years of age	0 cases	0 per cent

Our youngest case was 20 years old our oldest was 80 the average age at onset was 56 5 years

The age incidence of coronary thrombosis with cardiac infarction diagnosed clinically is much the same as that of angina pectoris The age groups of 461 cases analyzed by Bland and White (unpublished data 1936) are as follows

Clinical coronary thrombosis with myocardial infarction (age at onset)	Below 30 years of age	3 cases	0 7 per cent
	30 to 40 years of age	16 cases	3 5 per cent
	40 to 50 years of age	80 cases	17 4 per cent
	50 to 60 years of age	169 cases	36 6 per cent
	60 to 70 years of age	142 cases	30 8 per cent
	70 to 80 years of age	47 cases	10 2 per cent
	Over 80 years of age	4 cases	0 9 per cent

Our youngest case was 22 years old our oldest 81 the average age at onset of the entire series of 461 cases was 56 2 years Since the analysis of this series we have encountered in another series that of 100 cases under the age of 40, six patients all men under the age of 30 (Gertler, et al *1950) I have* seen still a few other patients under 30 years old the youngest was a 22 year old soldier with xanthomatosis Yater and his associates have reported 450 cases of men in military service who had fatal coronary heart disease as proved at autopsy between the ages of 18 and 39 years (Yater et al 1948) The youngest cases of atheromatous coronary thrombosis on record have been

a lad aged 12 years with diabetes (Shivelhood 1948) a girl aged 16 (MacDougall 1949) a boy 18 years old (Jamison and Hauser 1925) and a young woman of 19 (Evans and Graybiel 1948) One other case of progeria male aged 7½ died of coronary occlusion at the Massachusetts General Hospital (Talbot et al 1945)

And now very recently (1949) Gertler and Garn of our Massachusetts General Hospital coronary research group through the kindness of Drs J B Hamilton and C V Hawke have studied a large group of eunuchs and found among them a strikingly low incidence of coronary heart disease even in the older cases and also a very low blood cholesterol content

Coronary embolism though rare may occur at any age even in youth Two cases of cardiac infarction so caused under the age of 30 years have been reported by Parkinson and Bedford (1928) even in infancy cardiac infarction due to infectious embolism is on record (Schaps 1905) There are also two reports of paradoxical coronary embolism from a femoral vein thrombus in a man aged 35 years and in a woman aged 47 both without coronary disease (Saphir 1933 Jacobi et al 1934)

Sex The male sex is more often affected and to a more serious degree by coronary heart disease than is the female In a series of 200 clinical cases of cardiac infarction (Bland and White 1941) 168 (84 per cent) were male and 32 (16 per cent) were female while in a series of 83 postmortem cases of the same condition reported by Parkinson and Bedford (1928) 72 were male and 11 were female The ratio of males to females in Clawson s autopsied series of 1 215 cases of coronary heart disease (1941) was 4 2 to 1 The most interesting and highly significant ratio of all has been in two separate groups of 100 patients each under the age of 40 years with coronary heart disease with or without myocardial infarction the first group reported by Glendy Levine and White in 1937 and the second group under recent study by our research team at the Massachusetts General Hospital there were 96 males and only 4 females in the first group and 97 males and 3 females in the second These findings would appear to be of great significance in the consideration of the etiology of coronary heart disease and demand further analysis *Why should the robust and apparently most masculine young male be particularly prone to this disease?* Is there a sex difference in the metabolism of fat or in its deposition? Does the greater thickness of the coronary artery wall in the male than in the female infant reported by Dock (1946) and by Minkowski (1947) play a role? Is it a part of the law of the animal kingdom whereby the male is more vulnerable than the female with a shorter life span (Hamilton 1948) by 4 or 5 years in the U S A of recent years?

Other etiologic factors Race temperament social and economic status and occupation appear to have but slight bearing on the incidence of coronary heart disease At one time it was thought that coronary atherosclerosis was uncommon in the Negro but now increasing evidence thereof has been adduced by more adequate studies recent reports have been published by Hunter (1946) and Smith (1946) It is still stated that coronary thrombosis

is comparatively rare in the Chinese but similarly further studies thereof are needed

Certain symptoms associated with coronary disease namely angina pectoris and the pain and prostration of acute coronary thrombosis are more often found in sensitive mentally overworked and frequently robust or stout professional and business men than in other individuals Whether coronary thrombosis is actually more common in such persons has not yet been shown but one has the definite impression that it is less common in the lean laborer or farmer further study of this important point is however essential

One of the most impressive clues in our studies to date is anthropologic the majority of the young cases are not only male but mesomorphic (muscular type) there being no pure ectomorphs (very lean type) in the series although there are mixtures of mesomorphy with ectomorphy and, more often of mesomorphy with endomorphy (fat type with large abdomen) Does the muscular metabolism of the robust mesomorphic male play a role in the early development of serious coronary atherosclerosis? Especially so if he makes but little use of his muscles?

The effect of climate has not yet been adequately studied in relation to the incidence of coronary heart disease

Alcohol tobacco tea and coffee are probably without direct influence except that in occasional individuals the symptom of coronary insufficiency namely angina pectoris is precipitated or aggravated by excessive use of tobacco while heavy indulgence in alcohol over many years may have a damping influence on the symptoms but not otherwise on the ill effects of coronary heart disease

Heredity as already mentioned does appear to exert a definite action There may well be an inherited family coronary arterial tree in some families more branching and interlacing may occur than in others who are prone to develop coronary heart disease This important point needs accurate evaluation Probably however of more importance is the inheritance of body build that is of mesomorphy mentioned above and of a metabolic fault whereby atheroma is favored The hereditary predisposition to certain diseases which favor the occurrence of presenile coronary heart disease namely diabetes mellitus xanthomatosis and hypertension is certainly an important consideration Hereditary hypercholesterolemia and familial xanthomatosis in a series of 35 families (172 members) and 29 individuals with 40 per cent showing coronary heart disease constituted an inherited incomplete dominant trait (Adlersberg and Parets 1949) Familial liability to sudden coronary death was reported by Herapath and Perry in 1930 in the persons of a father aged 42 and of his three sons aged 43 31 30

Pathology A discussion of coronary artery atherosclerosis itself and of other coronary artery diseases has been presented under the preceding section of Etiology and need not be repeated here

The effect of coronary disease on the heart is extremely variable in degree and rapidity of involvement There may be only ischemia without structural

change there may be slight fatty degeneration generalized or local with a late sequela of slight fibrotic change there may be extensive changes due to single or multiple infarctions which are so gradual in development that the heart remains competent though with lowered reserve the fibrosis occurring in limited small or large areas or diffusely or there may be a suddenly developed myocardial infarct small or large fatal or outlived involving one part or another of the left ventricle rarely the right ventricle or both ventricles and due to *occlusion by thrombosis or embolism of one of the main coronary artery* branches The size of the infarct the prognosis the process of repair and the completeness of healing depend on several factors the size of the artery occluded the rapidity of occlusion the extent of either congenital or acquired anastomotic or collateral coronary circulation (and possibly also of other blood channels including the Thebesian circulation and extracardiac blood vessels in the pericardial attachments) and the effectiveness of treatment

The major and by far the most important source of the collateral coronary circulation that so often rescues the myocardium from anoxia is undoubtedly the multitude of small anastomotic arterial branches themselves which gradually grow larger and more and more competent to supply the need through the years

The Thebesian vessels are small channels opening into the heart chambers especially the ventricles of varying numbers and size they connect directly with coronary capillaries and veins and by sinuses with the arterioles and probably are the vestiges of the intertrabecular spaces of the primitive ventricle whereby blood was brought into contact with the cells of the myocardium before the development of an adequate coronary circulation These Thebesian vessels are of uncertain function and value but sometimes they and especially *other blood sinuses which link up various parts of the coronary circulation* may well be helpful when the regular channels of blood supply to the myocardium are obstructed as in rare reported cases in which life continues for a while in spite of complete and chronic occlusion of both coronary arteries in such cases however highly placed and anastomotic coronary arterial branches proximal to the points of block doubtless play the major role in maintaining the myocardial circulation Compensatory circulation to the myocardium by way of extracardiac vessels *developing over the pericardial attachments* or adhesions as from the bronchial arteries is probably sometimes available in addition to the blood supply via the Thebesian vessels and the myocardial blood sinuses but adequate blood vessels of the sort would seem to be rare this idea has however pointed to the possible value of artificially introducing blood supply from the outside and Beck and O Shaughnessy have done this in man the former using at first the pectoral muscle (1935) and the latter the omentum through the diaphragm (1937) work which still remains in the experimental stage and in which other technics are being tried (Beck 1948)

The descending branch of the left coronary artery near its mouth is the place most commonly affected both by extensive sclerotic change and by

thrombosis When there is a sudden occlusion at this spot an infarct usually appears in the anterior wall of the left ventricle near the apex and often involves also the anterior and lower part of the interventricular septum (Figure 106A) This is the commonest site of cardiac infarction and the descending branch of the left coronary artery has as a result of its lethal role been called the artery of sudden death The preponderance of involvement of this artery and of this part of the left ventricle is not however so great as used to be

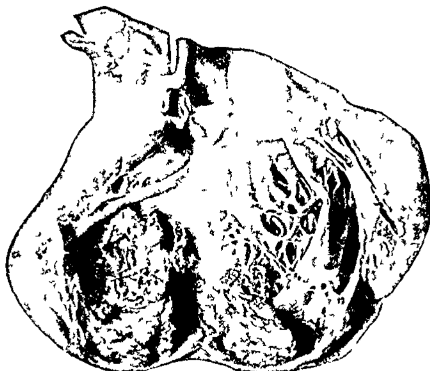


FIG 106A Photograph showing a large fibrosed cardiac infarct about four months old in the anterior and apical part of the left ventricle involving the septum and the base of the papillary muscles and resulting from thrombosis of the descending branch of the left coronary artery with mural thrombus in the cardiac aneurysm resulting from the infarct This lesion was found in a man 68 years old

believed it is only slightly in the lead The reason for the erroneous idea of some years ago was that a careful enough search was not always made for old scars at other sites and also because there was more often recovery from infarcts in other sites and patients leaving the hospitals were lost to view

The second most likely spot for infarction is the posterior wall of the left ventricle near the base behind the posterior cusp of the mitral valve due usually to occlusion of the right coronary artery or of the circumflex branch of the left (Figure 106B)

The relative frequency of thrombosis of the three larger coronary arterial trunks in a series of 49 cases of myocardial infarction found in 1 000 consecutive autopsies at the Mayo Clinic was as follows anterior descending branch

of the left in 28 cases right coronary 20 cases and circumflex branch of the left 17 cases (Barnes and Ball 1932) In that series of cases the infarct involved the apex and anterior portion of the left ventricle in 25 cases and the posterior basal portion of the left ventricle in 21 cases while the remaining 3 hearts showed two infarcts one at the apex and one at the base In another series of 34 cases (Saphir et al 1935) both coronary arteries were involved in all of the cases but the more severe lesions were found in the anterior descending branch of the left There was involvement of at least two coronary



FIG 106B Photograph showing a small fibrosed cardiac infarct (*A*) in the posterior wall of the left ventricle at the base just below the posterior cusp of the mitral valve (which is lifted up) Note the whitened thickened endocardium and the small patch of adherent pericardium (*B*) overlying the infarct. The left ventricular wall at the apex is somewhat thinner than usual but is not the site of any localized infarct From a man of 80 years of age the acute coronary thrombosis had occurred at the age of 63

branches supplying each infarcted area a fact of great significance in helping to explain various clinical electrocardiographic and pathologic anatomic discrepancies that have been noted in recent years An interesting and important observation in this study was that although in general there was agreement between the infarcted areas and disease of the particular arterial trunks directly supplying these areas occasionally a recent thrombus was found in one coronary artery while the most recent infarct was located in an area supplied by the previously occluded opposite artery obviously the area before becoming infarcted had been supplied by collateral anastomoses Further evidence of the very complicated state of affairs in coronary thrombosis has been supplied by Sprague and Orgain (1935) in an analysis of 3 889 autopsied cases

at the Massachusetts General Hospital 131 showed some degree of coronary occlusion but acute coronary thrombosis with occlusion limited to a single coronary artery or branch was found to be relatively infrequent only 17 of 61 cases of acute coronary thrombosis showing such limitation complete or recanalized thrombosis of a main artery or a main branch was discovered in the left coronary circulation in 46 cases and in the right in 21 In a recent analysis of a 20 year experience at the Massachusetts General Hospital the left coronary artery was found to be thrombosed much more commonly than the right and anterior wall infarcts were twice as common as the posterior and more serious, as evidenced by the fact that of the 23 cases of rupture 22 were through the anterior wall (Wang et al 1948)

It has remained for Blumgart and Schlesinger (1940) to clarify much more fully this hitherto confused and difficult problem of the relationship between coronary occlusion myocardial infarction and fibrosis and clinical manifestations by the study of 355 consecutive cases examined post mortem by special injection roentgenologic and dissection technic They concluded (1) that in normal hearts intercoronary anastomoses though present are of little functional significance in obviating the untoward effects of sudden coronary narrowing or occlusion (2) that the apparent inconsistency between the presence of long standing obstructive arterial lesions and the absence of significant pathologic or clinical evidence of myocardial damage was dispelled by the demonstration of a collateral circulation (which had gradually developed) serving as a by pass in relation to the obstruction in each of these hearts (3) that in some instances of acute myocardial infarction caused by acute coronary occlusion the fresh thrombus may be found distant from the infarct in a vessel serving as a source for the collateral circulation supplying that area (for example fresh infarction of the anterior wall of the left ventricle precipitated by a fresh occlusion in the right coronary artery which was serving as a source of collateral circulation to that area in the place of the old occluded anterior descending left coronary artery) and (4) that every patient suffering primarily from angina pectoris without evidence of valvular disease or arterial hypertension will show at postmortem examination old complete occlusion of at least one major coronary artery

Narrowing or occlusion of the smaller coronary branches may be completely compensated for by a rich collateral circulation often it is not so compensated however and small localized areas of infarction result which are without symptoms or signs unless an especially important part of the heart is involved such as the atrioventricular node (of Tawara) and bundle (of His) with the production of heart block Infarction of the base of the interventricular septum may lead to atrioventricular or intraventricular block or even to perforation of the septum

Cardiac infarction results from the blocking off of blood supply to a part of the heart There follows necrosis of the tissue (Figure 107) chiefly of the myocardium often also of the pericardium if the infarct is large enough to extend to this structure but infrequently of the endocardium which very probably receives

much of its blood supply directly from the ventricular chamber If the pericardium is affected a sterile fibrinous pericarditis occurs and if the endocardium is involved a thrombus is likely to form over it in the ventricular (or rarely atrial) cavity Most intraventricular thrombi after cardiac infarction



FIG 107 Microphotographs of myocardial infarcts secondary to coronary disease (*A*) Acute stage with invasion of leukocytes and beginning necrosis of muscle fibers (*B*) Subacute stage with almost complete disappearance of damaged muscle fibers and beginning organization of scar with several small blood vessels A few undamaged muscle cells remain near one of the small arteries (*C*) Old fibrous scar involving part of the myocardium and penetrating to the endocardium (to the left) (Kindness of Drs F B and Kenneth Mallory Massachusetts General and Boston City Hospitals Boston)

however are laid down in the more or less stagnant pockets (sometimes frank aneurysms) where the infarcted heart wall is thinned and noncontractile even though the endocardium itself is intact Such thrombi may form over old scars as well as over fresh infarcts (Mallory White and Salcedo Salgar 1939) It is from such intraventricular mural thrombi that emboli are frequently de tached to cause serious complications after acute coronary occlusion less often in the case of old scars it was largely to prevent such clots that anti coagulant therapy was introduced in the treatment of acute myocardial infarc tion Infarction of the atria is rare even if carefully looked for probably be cause the wall is thin and in large part supplied directly from the atrial cavities

If the patient survives the immediate shock of the coronary occlusion and the acute cardiac dilatation and failure that sometimes follow the process of repair begins and is complete after some weeks or months (depending on the size of the infarct and the adequacy of the circulation in its neighborhood) leaving a fibrous scar of greater or lesser extent (Figure 107) In the process of repair there occur thinning and weakening of the ventricular wall which lead not rarely to cardiac aneurysm and during the acute stage even to rupture with fatal hemorrhage into the pericardium

Rupture of the heart when not traumatic or due to uncommon infectious processes (abscesses) is caused by recent almost never by old cardiac infarc tion from coronary occlusion such a mechanism is responsible almost invari ably during the first ten to fourteen days of the infarct (Jetter and White 1944 Friedman and White 1944) In a series of 270 cases of myocardial infarction among 2 967 autopsies at the Massachusetts General Hospital be tween March, 1933 and November 1940 cardiac rupture was found in 10 (3 7 per cent) all among the 105 cases of fresh infarction (9 5 per cent) and none among the cases with old infarcts and the same percentage (9 5) was reported by Diaz Rivera and Miller in 1948 all in acute cases too this was in contrast to rupture of the heart in 16 (73 per cent) of 22 cases of acute myo cardial infarction among psychotic patients in whom both diagnosis and treat ment were difficult Rupture involves the ventricular septum in some cases actually 20 per cent of 76 among 28 657 autopsies reported by Furnam and Meneely (1948) it should be diagnosed correctly ante mortem although only five such were found among 36 collected in the literature by Rabinovich (1947) The papillary muscle may also rupture

Sometimes lime salts or even bone are laid down in the old necrotic area of the infarct as may also happen in a more gradual way in other parts of the heart from faulty circulation or disturbed metabolism producing masses of calcification in papillary muscles or stony rings at the bases of mitral and aortic valves

When there is marked narrowing of the coronary arteries with or without actual occlusion here or there angina pectoris and sudden death are quite com mon the myocardium itself may or may not show fibrosis or areas of infarc tion in such cases but it is always ischemic In their classic studies Blumgart

and Schlesinger (1937 1940) have presented evidence that temporary ischemia may cause irreversible myocardial changes and that if the ischemia is of sufficient duration even without acute vascular occlusion myocardial infarction may result of the same character and degree as that which occurs after permanent and complete coronary occlusion

The heart may or may not be enlarged as the result of coronary disease with simple sclerosis and little or no strain on the damaged heart there is no change or possibly even a slight decrease in size but with healing after a large infarction especially if there is much strain well marked enlargement may result Horine and Weiss (1935) who followed with roentgen ray study 20 patients who had a normal sized heart at the time of coronary thrombosis found no evidence of enlargement over a period of nine months to nine years and ten months but Bartels and Smith (1932) on the other hand in an autopsy study of the hearts of 42 cases of myocardial infarction in which all other known or supposed causes of cardiac hypertrophy (such as hypertension) were excluded found definite gross cardiac hypertrophy in 37 (88 per cent) the average increase in weight above the estimated normal being 132 gm My own experience is nearer that of Bartels and Smith but it is the size of the infarct and the presence or absence of complications that determine whether or not the heart will be enlarged when there is but a small infarct or angina pectoris alone without complications the size of the heart may remain within normal limits

Cardiac aneurysms ruptures of the heart cardiac infarcts old and new and fatty and fibrotic changes of lesser extent have been known to pathologists for centuries and their connection with coronary disease recognized post mortem for many years but in the practice of medicine these conditions have been regarded as of much clinical significance and possible to diagnose readily only during the present generation

Symptoms The production of symptoms in heart disease of coronary origin is dependent on several factors in particular the sufficiency of the coronary circulation with relation to the degree of activity to which the myocardium is subjected and also the speed of development of myocardial change the extent of the damage the adequacy of coronary arterial anastomoses the amount of strain on the damaged heart and the sensitiveness of the nervous system of the victim If coronary narrowing and obstruction and even cardiac infarction develop slowly and there is no excessive cardiac strain there may be no symptoms at all though there be extensive areas of damaged muscle and though one or both coronary arteries be occluded The reserve strength of both myocardium and its blood supply is normally very great and not easily exhausted

If however *sudden occlusion of a large coronary artery* occurs with inadequate collateral coronary circulation the symptoms may be extreme with terrible pain shock and sometimes death Between these two extremes of symptoms in coronary heart disease from none at all to those that are overwhelming there may be found all grades and varieties Sometimes the symp-

toms much exaggerated by nervousness or neurocirculatory asthenia in a particularly sensitive individual are out of all proportion to the amount of heart damage and disability

The two most common symptoms of coronary heart disease are pain and dyspnea It is difficult to obtain accurate figures for the relative frequency of these two symptoms since some old persons though limited by slight substernal oppression or dyspnea on exertion do not make much of these limitations which they ascribe to old age, they may even find it difficult to distinguish between substernal oppression and dyspnea On the whole oppression is the more common symptom and is due to the inability of the damaged coronary arteries to maintain an adequate circulation in the heart muscle Other symptoms also occur particularly palpitation, but they are less characteristic

Pain in coronary heart disease is of different sorts and degrees It may consist of slight moderate or severe, high, mid or low substernal oppression transient on exertion that is angina pectoris there may be extreme substernal and epigastric oppression lasting for hours and sometimes followed by collapse due to coronary thrombosis or there may be slight to moderate precordial aching due commonly to an associated neurocirculatory asthenia The precordial aching is more commonly found in other conditions than in coronary heart disease the angina pectoris is infrequently found in other conditions and the pain of coronary thrombosis is never like that found in other conditions except when it is atypical and so low in position that it simulates pain of gastrointestinal or gallbladder origin or in very rare cases may be mistaken for the pain of a dissecting aortic aneurysm or for that due to pulmonary embolism The transient oppression due to coronary insufficiency that is angina pectoris may almost exactly be simulated in position and character and duration by the discomfort due to spasm of esophagus or upper end of the stomach (cardiospasm) or indeed one symptom may excite the other the differentiation is generally quite clear in the positive relationship of angina pectoris to effort

The name angina pectoris (Latin *angina* from the Greek ἀγχόνη strangling and *pectus* breast bone or breast) was introduced by Heberden in 1768 to describe this characteristic symptom which has been also called stenocardia

Heberden William Some Account of a Disorder of the Breast *Medical Transactions* Royal College of Physicians London 1772 Volume 2 page 59 The original mention of angina pectoris was made by Heberden at a lecture before the Royal College of Physicians of London in July 1768 but not published until 1772

The entire lecture is herewith presented as published in 1772

There is a disorder of the breast marked with strong and peculiar symptoms considerable for the kind of danger belonging to it and not extremely rare of which I do not recollect any mention among medical authors The seat of it and sense of strangling and anxiety with which it is attended may make it not improperly be called Angina pectoris

"Those who are afflicted with it are seized while they are walking and more particularly when they walk soon after eating with a painful and most disagreeable sensation in the breast which seems as if it would take their life away if it were to increase or to continue the moment they stand still all this uneasiness vanishes In all other respects the patients are at the beginning of this disorder perfectly well and in particular have no shortness of breath from which it is totally different

"After it has continued some months it will not cease so instantaneously upon standing still and it will come on not only when the persons are walking but when they are lying down and oblige them to rise up out of their beds every night for many months together and in one or two very inveterate cases it has been brought on by the motion of a horse or a carriage and even by swallowing cough ing going to stool or speaking or by any disturbance of mind I have heard once and only one person say that he had known it attack him while he was up and standing still or sitting But most whom I have seen have been perfectly unaffected with riding in any manner with speaking swallowing laughing sneezing or vomiting One has told me that this complaint was greatest in winter another that it was aggravated by warm weather in the rest the seasons were not sus pected of making any difference

I have observed something like this affection of the breast in one woman who was paralytic and have heard one or two young men complain of it in a slight degree but all the rest whom I have seen who are at least twenty were men and almost all above 50 years old and most of them with a short neck, and inclining to be fat

When a fit of this sort comes on by walking its duration is very short, as it goes off almost immediately upon stopping If it come on in the night, it will last an hour or two and I have met with one in whom it once continued for several days during all which time the patient seemed to be in imminent danger of death.

When I first took notice of this distemper and could find no satisfaction from books I consulted an able physician of long experience who told me that he had known several ill of it and that all of them had died suddenly This observation I have reason to think is generally true of such patients having known six of those for whom I have been consulted die in this manner and more perhaps may have experienced the same death which I had no opportunity of knowing But though the natural tendency of this illness be to kill the patients suddenly yet unless it have a power of preserving a person from all other ails it will easily be believed that some of those who are afflicted with it, may die in a different manner since this disorder will last as I have known it more than once near twenty years and most usually attacks only those who are above fifty years of age I have accord ingly observed one who sunk under a lingering illness of a different nature

The os sterni is usually pointed to as the seat of this malady but it seems some times as if it was under the lower part of it, and at other times under the middle or upper part but always inclining more to the left side and sometimes there is joined with it a pain about the middle of the left arm What the particular mischief is which is referred to these different parts of the sternum it is not easy to guess and I have had no opportunity of knowing with certainty It may be a strong cramp or an ulcer or possibly both.

"The opinion of its being a convulsion of the part affected will readily present itself to any one who considers the sudden manner of its coming on and going off the long intervals of perfect ease the relief afforded by wine and spirituous

cordials the influence which passionate affections of the mind have over it the ease which comes from varying the posture of the head and shoulders by straightening the vertebrae of the thorax or by bending them a little backwards or forwards the number of years which it will continue without otherwise disordering the health its generally bearing so well the motion of a horse or carriage which circumstance often distinguishes spasmodic pains from those which arise from ulcers and lastly its coming on in certain patients at night just after the first sleep at which time the incubus convulsive asthmas numbness epileptics hypochondriac languors and other ills justly attributed to the disturbed functions of the nerves are peculiarly apt either to return or to be aggravated

'The pulse is at least sometimes not disturbed by this pain and consequently the heart is not affected by it which I have had an opportunity of knowing by feeling the pulse during the paroxysms but I have never had it in my power to see any one opened who had died of it the sudden death of the patients adding so much to the common difficulties of making such an enquiry that most of those with whose cases I had been acquainted were buried before I had heard that they were dead

But thought it be most probable that a strong spasm be the true cause of this disorder yet there is some reason for thinking that it is sometimes accompanied with an ulcer and may partly proceed from it for I have seen two of these patients who often used to spit up blood and purulent matter one of whom constantly asserted that he felt it come from the seat of the disorder Another had a painful sensation in swallowing and upon pressing the part which seemed to be affected From a fourth who fell down dead without any notice there immediately arose such an offensive smell as made all who happened to be present judge that some foul abscess had just then broken

Bleeding vomits and other evacuations have not appeared to me to do any good Wine and cordials taken at going to bed will prevent or weaken the night fits but nothing does this so effectively as opiates Ten fifteen or twenty drops of Tinctura Thebaica taken at lying down will enable those to keep their beds till morning who had been forced to rise and sit up two or three hours every night, for many months Such a quantity or a greater might safely be continued as long as it is required and this relief afforded by opium may be added to the arguments which prove these fits to be of a convulsive kind Time and attention will undoubtedly discover more helps against this teizing and dangerous ailment but it is not to be expected that much can have been done towards establishing the method of cure for a distemper hitherto so unnoticed that it has not yet as far as I know found a place or a name in the history of diseases

Later Heberden added more cases of angina pectoris to his twenty-odd mentioned in the original lecture quoted above and in 1786 in a chapter entitled Pectoris Dolor in his *Commentaries on the History and Cure of Diseases* (which was translated and published by his son William Heberden Jr in 1802 a year after his own death) he wrote as follows I have seen nearly a hundred people with this disorder out of which number there have been three women

Although coronary thrombosis is more likely than not to be attended by severe exhausting crushing substernal pain often radiating to either arm or both arms neck head or back as in angina pectoris there are exceptions without any pain at all in such cases there may be dyspnea instead or simply

collapse or prostration In some groups of cases of coronary thrombosis the incidence of pain may be surprisingly low as in one series of 76 patients with coronary thrombosis proved at postmortem examination in which only 36 (47 per cent) gave a history of pain 29 (38 per cent) gave a history of no pa n and the remaining 11 died suddenly (Davis 1932) in another group of 100 cases reported by Gorham and Martin (1938) cardiac pain was noted in 58 per cent In my own experience however pain is more common than indi cated by these figures a review of 56 consecutive unselected cases of my own proved at autopsy has revealed the occurrence of pain in all but two (96 4 per cent) severe in 34 (61 per cent) moderate in 10 (18 per cent) and mild in 10 (18 per cent) (with the help of Dr F W Miskall) The pain may be quickly masked by collapse or a moribund state or concealed by other symptoms or even by medication or alcoholism or indeed on occasion not ade quately sought for

The similarity of the character and the position of the pain of coronary occlusion to that of paroxysmal angina pectoris is a strong argument that coronary disease by limiting the blood supply to the heart muscle is the com mone t cause of angina pectoris

Dyspnea may vary from a slight breathlessness on exertion to the awful struggling respiration of marked cardiac asthma dependent on the severity and suddenness of failure of the involved left ventricle which causes vascular engorgement of the lungs Finally instead of pain as classically described a sudden onset of dyspnea with or without pulmonary edema or of Cheyne Stokes respiration may also occur as an accompaniment of left ventricular weakness due to acute coronary occlusion or to chronic coronary heart dis ease particularly in individuals with very limited myocardial reserve to start with Moreover angina pectoris sometimes initiates such dyspneic attacks Sigh- ing respiration noted in occasional cases is due to the nervous state of the patient and not to his heart disease

Palpitation is frequently complained of by patients with coronary heart disease chiefly because of the occurrence of arrhythmia Such arrhythmia is usually of relatively little importance consisting as it does for the most part of premature contractions chiefly of ventricular origin However two addi tional observations should be made regarding premature beats and coronary heart disease in the presence of coronary insufficiency premature beats may on occasion be painful due doubtless to the short diastolic rest and secondly premature beats induced by exercise suggest the possibility of an underlying deficiency of the coronary circulation Occasionally paroxysmal auricular tachycardia and atrial fibrillation are also found as complications of coronary heart disease they are somewhat more important than premature beats Fi nally paroxysmal ventricular tachycardia and atrioventricular block either partial or complete are the most serious disorders of mechanism which may occasion palpitation the former is particularly of ill omen but fortunately very rare These two disturbances of the heart beat will be discussed in Chapters 32 and 34 respectively

Prostration or collapse, sometimes of high degree is a frequent early symptom of acute coronary occlusion due to a state of vasomotor shock or peripheral vascular failure which may in itself be fatal in a few cases prostration like dyspnea may replace pain as the chief symptom of acute myocardial infarction especially in very old persons Syncope as a much less important nervous reaction may be a rare complication even in angina pectoris and as such was once unnecessarily and confusingly designated syncope anginosa (Parry 1799)

Other symptoms occurring with coronary heart disease are either infrequent unimportant or due to complications General weakness is occasionally seen in older persons who have arteriosclerosis elsewhere The same is true of mental disturbances faintness dizziness and even coma and convulsions except that cerebral anemia due to high grade heart block resulting from coronary disease may give rise to the *Adams Stokes syndrome* (faintness syncope and convulsions with a slow pulse) Prolonged coma lasting for hours or days especially in aged persons may follow rarely the temporary or prolonged drop in blood pressure that sometimes accompanies acute coronary thrombosis Congestive failure may result in cough hemoptysis gastrointestinal symptoms ascites and edema Sweating restlessness and vomiting are common symptoms at the onset of coronary thrombosis the vomiting however is more often induced by the opiate used in treatment than by the heart attack per se Hiccough is rare

Coronary thrombosis leading to myocardial infarction usually causes *fever* for a few days with a temperature rising to 101° or 102° F rectally the grade and duration depending on the size of the infarct undergoing necrosis (Figure 108) Also the cardiac lesion may give rise acutely to various local pains due to visceral cerebral or peripheral embolism resulting from the discharge into the circulation of pieces of the mural thrombus in the left ventricle pulmonary embolism may occur from thrombosis in the veins of legs or pelvis or from thrombi in the right ventricle whether due to right ventricular (usually septal) infarction or to stasis

Signs There are frequently no signs of coronary heart disease and the patient may give the appearance of perfect health This is especially true in the case of uncomplicated angina pectoris on effort When there is however a high degree of coronary insufficiency there is often a rather characteristic sallow unhealthy tint to the skin suggesting on occasion slight jaundice or anemia The patient is sometimes an obviously sick man at first glance and this is particularly true during the state of shock that may occur at the time of an acute extensive coronary thrombosis

A considerable amount of coronary disease may exist with little or no cardiac enlargement but a very large myocardial infarct or congestive failure whether limited to the left ventricle or involving the entire heart is always attended by cardiac enlargement easily found both by physical examination and by roentgen ray The enlargement may come rapidly with cardiac infarction it then consists chiefly of dilatation of the left ventricle but it may involve

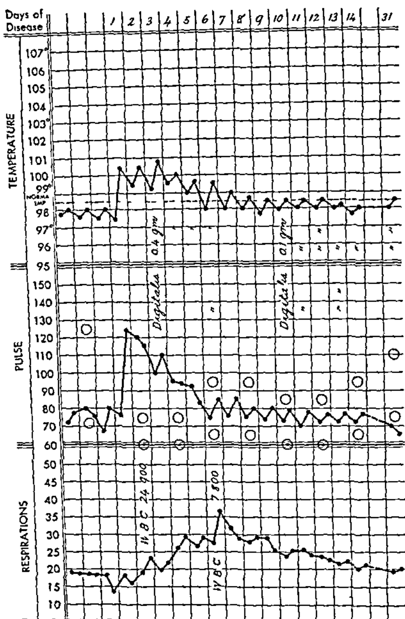


FIG 108 Chart in acute coronary thrombosis causing a large cardiac infarct showing temperature (mouth) pulse rate respiratory rate and blood pressure The patient male, 52 years old was in bed under observation and treatment for angina pectoris decubitus when the myocardial infarction occurred He recovered but died suddenly a year later Digitalization was carried out with beneficial results upon the onset of dyspnea due to dilatation and failure of the left ventricle The blood pressure is desig nated by circles open for systolic pressure and dotted for diastolic The leukocytosis at onset was unusually high but quickly subsided

also the right ventricle when the left ventricle fails as the process of repair goes on hypertrophy develops being apparently a compensatory measure From coronary heart disease (thrombosis with infarction) alone the heart may increase in weight to 500 or 600 gm (normal weight about 300 gm)

The heart sounds are frequently weakened in coronary heart disease especially *the first sound at the apex shortly after coronary thrombosis sets in* sometimes a so-called tic tac rhythm results from this weakening of the first sound Gallop rhythm protodiastolic in time is especially common with left ventricular dilatation and weakness following coronary thrombosis Reduplications and gallop rhythm may also occur with the development of intraventricular and atrioventricular block The pulmonary second sound becomes accentuated if the left ventricle fails Murmurs may or may not occur the commonest is that of functional mitral regurgitation due to dilatation—an apical systolic murmur Basal murmurs are less common in coronary heart disease an aortic systolic murmur may be found due to aortic dilatation resulting from an associated hypertension Sometimes such a murmur is due to slight aortic stenosis caused by sclerotic involvement of the aortic valve, if aortic stenosis is marked with systolic thrill felt over the aortic area it is rarely to be ascribed to a simple atherosclerotic change in the aortic valve but more often to the result of an old infectious process with superimposed calcification An aortic diastolic murmur is not found in coronary heart disease unless there is a complication of syphilitic aortitis aortic stenosis with regurgitation chronic hypertension with dilated aortic valve ring or rarely senile ectasia of the aorta (see Chapter 28)

A pericardial friction rub frequently accompanies cardiac infarction especially if the infarct is large it appears usually on the second or third day of illness and is transient disappearing in a day or two—rarely it lasts for a week or more

The arrhythmias found in coronary heart disease have already been mentioned (see page 541) the most common being premature beats and atrial fibrillation *the atrial fibrillation is either paroxysmal (about 33 per cent)* or permanent (67 per cent) in type

The pulse rate varies widely in coronary heart disease from a normal range in most cases to a tachycardia of 120 or more in some cases with vasomotor shock or congestive failure in acute coronary thrombosis or with abnormal rhythm rarely there is a bradycardia which may be marked (down to 30) if high grade heart block supervenes

The blood pressure in uncomplicated coronary heart disease is normal or low Severe cardiac infarction following coronary thrombosis is however characteristically attended by a sharp fall in systolic blood pressure whether or not it has previously been high (because of hyperpiesia) The low blood pressure of 75 to 100 mm mercury systolic and 50 to 75 diastolic may continue for days, tending gradually to resume the level that existed before the coronary thrombosis or a somewhat lower level it is the combined result probably of vasodilatation myocardial weakness sedative drugs and rest In

a few cases the blood pressure is elevated by the pain during the acute episode of infarction I have encountered cases whose blood pressure was normal before and after the acute coronary occlusion but considerably increased at the time of the attack In a good many other patients with small- and medium sized infarcts the blood pressure is unaffected except for slight reduction with bed rest During periods of higher degrees of coronary insufficiency (sometimes lasting for weeks) the diastolic pressure may be slightly elevated (to 95 100 or 105 mm)

Roentgenologic study may show no abnormality whatsoever though the aorta is often distinctly tortuous and elongated from atheroma with prominence of the knob and sometimes with visible calcification Roentgen ray examination usually shows cardiac enlargement after myocardial infarction and sometimes a bulge at or just above the apex due to a cardiac aneurysm (Figure 125 page 657) In the case of extreme cardiac infarction the action of the heart may be obviously weak and the pulmonary artery and lung hilus shadows may be prominent due to pulmonary vascular engorgement secondary to failure of the left ventricle Fluoroscopy and kymography often reveal the site of the infarct as comprising a section of the left border of the heart shadow which shows little or no systolic pulsation or indeed even a paradoxical out thrust instead of retraction in systole in such cases as a rule however the diag nosis is obvious by other methods of examination

Calcified coronary arteries can sometimes be made out on the roentgenogram but this finding is of little or no clinical value since serious coronary heart disease may occur without it and since coronary calcification can be present without coronary insufficiency due to an adequate collateral circula tion Roentgen visualization of the coronary arteries is possible by retrograde aortic or arterial injection of contrast (Diodrast) fluid or by direct left ven tricular puncture (see Chapter 7) but it would seem to be unwise to subject cases suspected of having coronary heart disease to a possible hazard in this procedure

Electrocardiograms are of the greatest importance They are often normal with slighter degrees of coronary heart disease especially between (not dur ing) attacks of angina pectoris but in advanced coronary heart disease they usually show changes in the *Q* and *T* waves and often in the *S T* segments less frequently they show the presence of intraventricular block and low volt age uncommonly there is atrioventricular block The commonest cause of heart block is coronary disease Other disturbances of the heart beat are readily shown by electrocardiography Left ventricular preponderance is not com monly found unless there is an associated hypertension it may however fol low myocardial infarction with left ventricular hypertrophy and dilatation

There are a few relatively simple comments to make about the fundamental principles of electrocardiography in coronary heart disease before discussing detailed patterns In the *first* place there may be areas small or large of myocardium affected by the faulty blood supply sometimes the area is so microscopic that it may not show at all unless nodal or a v conduction tissue

is involved or such a large area or multiple areas are affected that the picture is very complicated one lesion neutralizing or confusing somewhat the effects of another It is surprising that so often the patterns are so clear-cut indicating isolated or preponderant lesions In the *second* place an effect on the electro cardiogram may be transient due to ischemia as during angina pectoris (Figure 109) or a combined effect of ischemia and of a destruction of muscle old or new also In the *third* place it is often possible to focus accurately over the

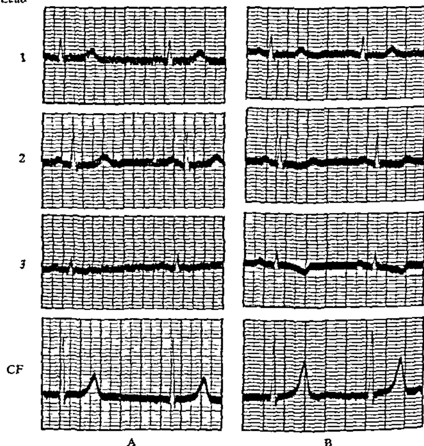


FIG 109 Electrocardiograms taken during an attack of angina pectoris (*B*) and while free from pain (*A*) male age 52 Note depressed *S T* segments in Lead 2 sharp inversion of *T* waves in Lead 3 and unusually high *T* waves in Lead CF of the record during angina pectoris Time = 0 04 and 0 20 second amplitude 1 mm = 0 10 mv

area involved by unipolar leads around the chest wall or in the esophagus or in the heart itself (by catheterization) which illustrates the value of multiple chest leads in fact even more on occasion than the six that have been routinely adopted And here I would urge the use of the V leads of Wilson rather than those using one extremity as the indifferent lead point (see Chapter 9) In the *fourth* place it is important to remember that a myocardial lesion

is a dead or blind spot or window and so reflects the action current elsewhere especially through the heart in the focus of the lead this accounts for the presence of a *Q* wave and the loss of an *R* wave (intrinsic deflection) over a myocardial scar In the *fifth* place the left ventricle is where most of the effects of coronary obstruction are to be found most commonly in the anterior wall but quite often in the posterior wall and septum too and even in the lateral wall although that is more often involved with either an anterior or posterior wall lesion the right ventricle and the atria are per se uncommonly involved quite possibly because of their thinner walls which are more readily supplied by the intracardiac blood stream or by a richer coronary network or both *Finally* the electrocardiogram may change slowly or unexpectedly in coronary heart disease and therefore isolated reco ds are often valueless serial records are not only desirable but often essential even daily for weeks

With these introductory remarks one may mention some of the coronary patterns but for details and many illustrations the reader is perforce referred to textbooks on electrocardiography or on coronary heart disease per se The earliest effect of coronary insufficiency on the electrocardiogram whether due to temporary ischemia or muscle destruction is an alteration of the baseline of the *S T* segment (current of injury) (Smith 1918 Pardee 1920) This consists of an elevation of one or more millimeters (0 1 millivolt) immediately over the muscle affected and a depression over the opposite part of the heart

Thus precordial Leads V_4 and V located over an anterior wall infarct will show an elevated *S T* segment during its early stage (Figure 110 page 548) and an esophageal lead (over the posterior wall) a depressed *S T* segment In the case of a posterior wall infarct Lead V_4 or V_5 will show a depressed *S T* segment in the earliest stages (Figure 111 page 549)

Meanwhile the bipolar classical limb leads reflect these various changes reciprocally in Leads 1 and 3 (Figures 112 and 113) altered by a vari able position of the heart a fresh anterior wall infarct is likely to raise the *S T* segment in Lead 1 and depress it in Lead 3 while a fresh posterior wall infarct may lower the *S T* segment in Lead 1 and raise it in Lead 3 These characteristic patterns quickly evolve within a few days with a return of the *S T* segments to the baseline and an inversion of the *T* waves in Leads V_4 V and 1 in the case of an anterior infarct (Figure 110) and upright (normal) *T* waves in Leads V_4 V and 1 but inversion (or increased inversion) of the *T* waves in Lead 3 (and often in Lead 2) (and in the esophageal lead) in the case of a posterior infarct (Figure 111) Finally with a large anterior myocardial infarct the *R* (intrinsic deflection) disappears and is replaced by a *Q* in Leads V_3 V_4 and V a *Q* wave appears in Lead 1 along with persistence of inversion of the *T* wave for awhile or permanently (Figure 114) while with a large posterior myocardial infarct a *Q* appears or deepens in Lead 3 and at times in Lead 2 with persistence of inversion of the *T* waves in those leads for awhile and sometimes permanently (Figure 111 B) an esophageal lead in the case of a posterior infarct would show a *Q* wave and inverted *T* wave while the anterior precordial Leads V_4 to V_6 inclusive tend to be normal The

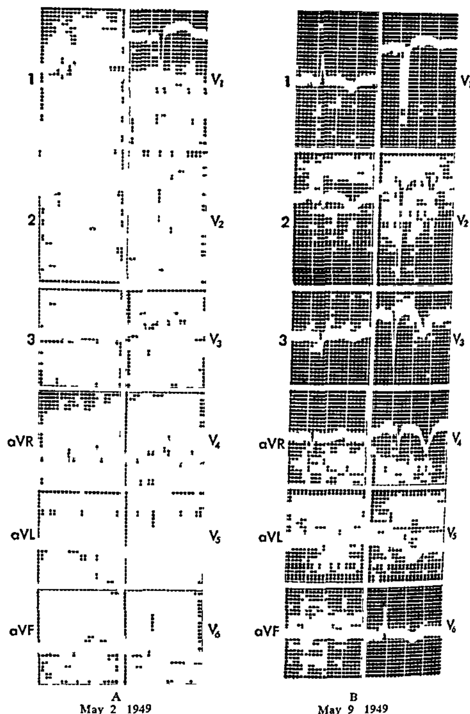


FIG 110 Electrocardiogram in anterior myocardial infarction acute stage and later Female age 45 Note especially the absence of *R* waves in Leads V to V inclusive in both *A* and *B* the elevated *S T* segment in Leads 2 V, V and V of *A* and the late inversion of *T* waves in Leads 1 2 and V to V inclusive of *B* Time = 0 04 and 0 20 second amplitude 1 mm = 0 10 mv

Q wave appearance (which is not constant) and the T wave inversion gave rise originally to the expressions Q_1T_1 and Q_3T_3 types of infarction (Parkinson and Bedford 1928) even before the exact sites of the infarction were identified The T waves may or may not revert to normal in time but the Q waves remain as permanent evidence of the scars

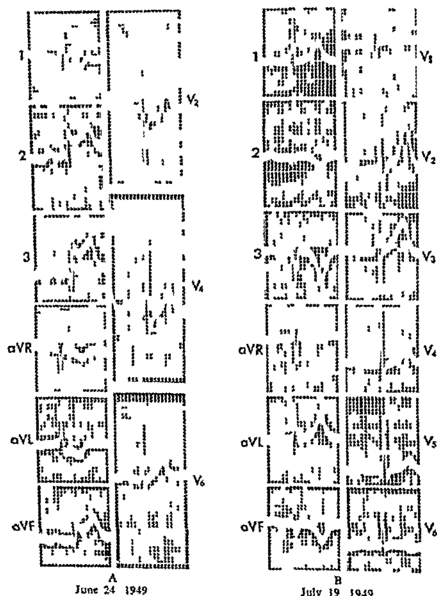


FIG 111 Electrocardiogram in acute posterior myocardial infarction male age 71 Note especially the greatly elevated S T segments in Leads 2 3 and aVF and the depressed S T segments in Leads 1 and aVL in A and the Q waves and inverted T waves in Leads 2 3 and aVF in B Time = 0 04 and 0 20 second amplitude 1 mm = 0 10 mv

The commonest patterns of myocardial ischemia and infarction have been presented but there are two other sites which may occasionally be identified by electrocardiogram and still rarer ones (e g in atria or right ventricle) that require more exploration A lateral wall infarct may show itself but little if it



FIG 112 Electrocardiogram in a case of anterior myocardial infarction showing reciprocal *S T* changes in Leads 1 and 3 and *Q* waves and inverted *T* waves in Lead V_s. Male age 54 (*A*) Bipolar limb leads 1 2, and 3 (*B*) unipolar limb leads *aVR aVL*, and *aVF* (*C*) six precordial leads V to V inclusive. Time = 0 04 and 0.20 second amplitude 1 mm = 0 10 mv

is small Lead V_6 or V_7 may then reveal it by change in $S\,T$ segments and T waves As a part of a larger infarct anterior or posterior it is easily identified (Figure 115) A septal infarct is also commonly associated with anterior or



FIG 113 Electrocardiogram in a case of posterior myocardial infarction occurring 48 hours previously and showing reciprocal $S\,T$ changes Note also Q waves and inverted T waves in Leads 2 3 aVF and V_6. Male age 50 (*A*) Bipolar limb leads 1 2 and 3 (*B*) unipolar limb leads aVR aVL, and aVF (*C*) six precordial leads V_1 to V inclusive Time = 0 04 and 0 20 second amplitude 1 mm = 0 10 mv

posterior wall infarction but shows itself by changes in the precordial leads to the right of usual left ventricular lead points that is in V and V_3 where changes in S T segments T waves and Q and R deflections are found similar to those described for other infarct sites (Figure 116 page 554)

The unipolar limb lead records are less important as a rule than the precordial or bipolar limb curves in the case of coronary heart disease They show

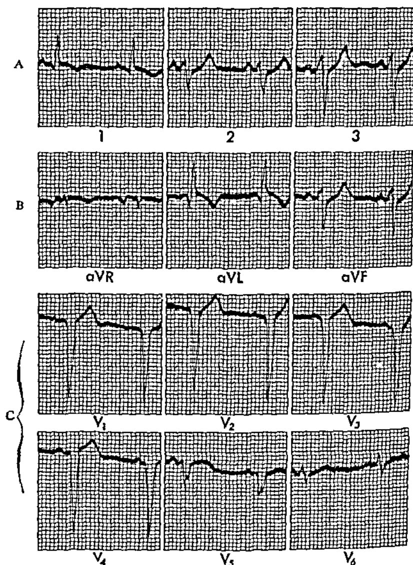


FIG 114 Electrocardiogram in a case of chronic anterior myocardial infarct male age 65 (A) Bipolar limb leads 1 2 and 3 (B) unipolar limb leads aVR aVL, and aVF (C) six precordial leads V to V inclusive Note especially Q waves and inverted T waves in Leads 1 and aVL and absence of R waves in Leads V to V inclusive Time = 0 04 and 0 20 second amplitude 1 mm = 0 10 mv

patterns which vary with the heart position and so give information about both position and myocardial state For example an anterior infarct in the case of a horizontal heart will give upright *QRS* and *T* waves in Lead VR and inverted *QRS* and *T* waves in Lead VL while an anterior infarct in the case of a vertical heart will give upright *QRS* and *T* waves in Lead VF the limb (left arm or left leg) facing the infarct showing the most abnormality For other discussion of precordial leads the reader is referred to Chapter 9

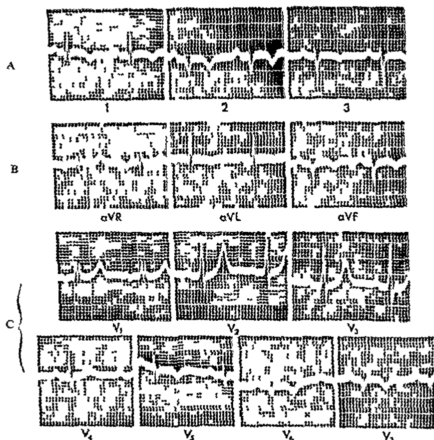


FIG 115 Electrocardiogram in a case of lateral infarct occurring one month previously male age 57 (*A*) Bipolar limb leads 1 2 and 3 (*B*) unipolar limb leads aVR aVL, and aVF (*C*) seven precordial leads V to V inclusive Note especially *Q* waves in Leads 1 2 V_6, and V absence of *R* waves in Leads 2 V_4, and V and inverted *T* waves in Leads 1 ^ 3 aVL aVF and V to V inclusive Time = 0 04 and 0 20 second amplitude 1 mm = 0 10 mv

Other methods of examination reveal little of importance as a rule though the grade and duration of leukocytosis resulting from sudden cardiac infarction is a useful clue to the size of the infarct and hence to the prognosis Usually a polymorphonuclear leukocytosis of 12 000 to 15 000 is found for three or

four days beginning a few hours after the onset of illness with an extensive infarct the white blood cell count may rise to 20 000 or more and remain elevated for a week or two The sedimentation rate of the red blood cells is accelerated in acute myocardial infarction and remains rapid for weeks until the healing process is well established

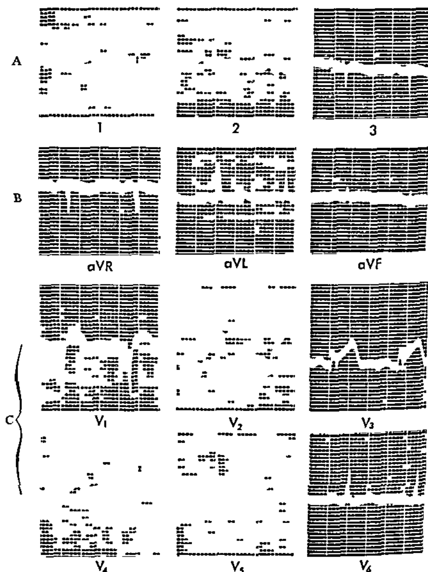


FIG 116 Electrocardiogram in a case of septal infarct female age 55 It is of interest that the limb leads show relatively little change while leads V and V are very abnormal with absence of *R* waves in V and elevated *S T* segments in V and V (*A*) Bipolar limb leads 1 2 and 3 (*B*) unipolar limb leads aVR aVL and aVF (*C*) six precordial leads V to V inclusive Time = 0 04 and 0 20 second amplitude 1 mm = 0 10 mv

Course and prognosis The course and prognosis of coronary heart disease are so variable that they must be considered individually in every case The condition unsuspected in life may be discovered only on postmortem exami nation after a noncardiac death in ripe old age or symptoms and signs may be marked and obvious in a fulminating acute catastrophe of severe coronary occlusion cutting off the blood supply to a large mass of heart muscle that may kill in a few hours or a few days The prognosis depends not only on the degree and speed of involvement of the myocardium but also on the treat ment the reserve strength of the heart and complications

When myocardial infarction sufficiently serious to be clinically recognized occurs the prognosis must always be guarded most cases however survive the immediate attack and half of the total survive for years a good many even for ten years or more The first week is much the most hazardous but danger of sudden death still exists during the second week even though all seems to be going well after the first fortnight of acute myocardial infarction recovery is the rule Of the series of 200 cases followed by Bland and White (1941) up to the time of death or with survival for over 10 years 38 (19 per cent) succumbed during the first month while 50 (25 per cent) have lived more than 10 years a much better record than was thought possible a decade ago The longest lived proved case recorded to date survived nearly 40 years after his first attack of myocardial infarction at the age of 40 and kept at work till he was 77 (Drake 1940) bettering the previous records of 17½ and 24½ years reported by myself in 1933 and 1937 records which had brought cour age to many victims of this common condition Just recently (1949) I re-examined a man whom I had seen at home 22 years earlier during a severe attack of acute myocardial infarction at the characteristic age of 52 years Despite slight cardiac enlargement and an abnormal electrocardiogram he has been in excellent health for many years and plays 18 holes of golf without symptoms several times a week at 74 years of age he continues well in 1951 Undoubtedly long survivals are frequent though recognized only relatively recently

The prognosis is made worse in coronary thrombosis by the following find ings advanced age a state of shock an abrupt and prolonged marked fall in blood pressure duration of severe substernal pain for more than twenty four hours fever for a week or more especially when high at the onset (103 to 104 F) a high leukocytosis especially if maintained for more than a week rapid and marked cardiac dilatation gallop rhythm ventricular paroxysmal tachycardia heart block pulsus alternans pulmonary edema with or without cardiac asthma dropsy and embolic phenomena It has been noted that the symptom of angina pectoris tends to disappear when congestive failure or atrial fibrillation sets in or after coronary thrombosis although angina pectoris may recur later It seems likely that this subsidence of angina pectoris is due in the case of congestive failure chiefly to restriction of activity of the patient and in the case of myocardial infarction to the death of the muscle involved

Paroxysmal coronary insufficiency as evidenced by the symptom of angina

pectoris on effort or even at rest (decubitus) has also like myocardial infarction a better prognosis than once was conceded Many cases were in the past ruled out of consideration because they recovered for it was not realized that there could be such an evolution More careful analysis and longer follow up of larger numbers of cases have doubled our expectation of the duration of life from an average of 4 to 5 years after the first symptom to one of 9 to 10 years (White Bland and Miskall, 1943) The explanation for such longevity and frequent recovery lies in the development of a more adequate collateral coronary circulation a fortunate provision of nature A recent follow up report of 3 440 cases of angina pectoris listed 405 who had survived ten years or more (Montgomery, et al , 1947)

Complications In addition to such complications as myocardial infarction cardiac aneurysm cardiac rupture congestive failure heart block and other arrhythmias and embolism from intracardiac mural thrombosis coronary heart disease is frequently accompanied by hyperpiesia and general arteriosclerosis sometimes by chronic rheumatic valvular disease diabetes nephritis and cerebral hemorrhage or thrombosis and less often by syphilitic aortitis thyroid disease (either thyrotoxicosis or hypothyroidism) bacterial endocarditis and congenital defects It should be added that although general or peripheral arteriosclerosis and coronary disease are often associated they frequently occur independently of each other One of the commonest of complications is indigestion chiefly cardiospasm with gaseous distention of stomach or bowels but sometimes gallbladder disease with or without stones infrequently there is peptic ulcer The cardiospasm is largely reflex and not primary but the gallbladder disease is definitely more common in persons with considerable coronary disease than in those without and vice versa (Walsh Bland Taquini and White 1941) this association is to be attributed not to a mutual causative effect but to some common factor dependent largely on the aging process in the type of persons affected Finally even in the later years of life nervousness and neurocirculatory asthenia may occur to exaggerate the symptoms of coronary heart disease and mental depression is frequently precipitated by the disability attending angina pectoris and particularly by the acute illness of myocardial infarction and the long but necessary convalescence especially in the case of a strenuous middle aged professional or business man never ill before

Treatment *Rest* Of prime importance is limitation of activity to suit each individual case For acute myocardial infarction such rest should be more or less complete for a few weeks more will be said about this below For angina pectoris decubitus the rest should be almost as complete until the condition ameliorates since acute coronary thrombosis is almost invariably the cause even though myocardial infarction may not follow Even for angina pectoris on effort alone it is often well at the onset to prescribe rest at home though not in bed until it is possible to appraise the situation adequately to determine the degree of chronicity of the disease and to plan future action

Drugs There is no specific treatment for coronary heart disease per se

unless it is due to syphilis a rare cause except for the quick relief of acute coronary insufficiency (angina pectoris) by the nitrites The iodides which have been used empirically for general arteriosclerosis appear clinically to be inert although experimental animals have been protected somewhat from atherosclerosis induced by high cholesterol diets when given potassium iodide A definite increase of the coronary flow by vasodilatation has been reported experimentally from the use of theobromine and especially theophylline ethyl ene diamine (aminophylline) and occasionally favorable effects on angina pectoris and dyspnea have been noted clinically after the use of these drugs Their trial is justified but unless improvement is noted in the course of a week or two their continuance is not worthwhile they are more likely to be effective when the coronary arteries are still able to dilate than in the case of rigid tubes They may be administered by mouth in the dose of 10 gr 0 6 gm of theo bromine (or 15 gr 1 gm of theobromine sodium salicylate Diuretin) three times daily, or preferably of 1½ to 3 gr 0 1 to 0 2 gm of theophylline ethylene diamine (aminophylline) three to five times a day The theophylline ethylene diamine (aminophylline) may be much more effectively given intravenously (0 24 gm in ampoule) or by suppository two or three times daily over short periods of time the intramuscular injection is often painful

Other drugs which have been recommended for the treatment of coronary atherosclerosis and for their effects on the heart have been in general disappointing in fact often inert Atropine was introduced hopefully to counteract a possible vagal factor in the production of coronary heart disease in man having been shown to be effective in dogs but its value has not been demon strated Choline and other lipotropic agents have been most recently used to delay prevent or even reverse somewhat the atheromatous process they are effective in certain animals especially the rabbit but they have not yet passed in man beyond the experimental stage Papaverine has been somewhat helpful in reducing the symptoms in particular the pain in coronary heart disease in the dosage of 0 03 to 0 09 gm (½ to 1½ gr) of the hydrochloride by subcutaneous injection twice daily or 0 09 to 0 20 gm (1½ to 3 gr) by mouth four times a day (Elek and Katz 1942) but it is often disappointing Testosterone has little or no value unless there is a specific endocrine need thereof The same is true of vitamin E and other vitamins Tissue extracts in general have been of little value Cactus is inert Cobra venom has been recommended for intractable pain but has not become established

One of the newly introduced drugs for the prophylaxis of angina pectoris apparently by the production of vasodilatation is khellin an active principle from the seeds of visnaga a plant growing in the Eastern Mediterranean area given in the dosage of 100 mg intramuscularly daily or 50 mg by mouth one to three times a day (Anrep et al 1947 1949 Armbrust and Levine 1950) in larger dosage this drug may cause nausea although its therapeutic effect has seemed favorable it is often toxic and needs further appraisal before widespread routine adoption

Perhaps the most useful drugs to date for obstinate severe angina pectoris

both introduced to depress thyroid function have been thiouracil or better methylthiouracil (0 2 to 0 6 gm daily) and irradiated iodine to accomplish a medical thyroidectomy (Blumgart Freedberg et al 1948 1950) The latter procedure offers the greater promise with less hazard of the first 18 cases tried (of coronary or myocardial insufficiency more commonly the former) 6 have proved to be highly successful and 6 others improved while 6 were failures the dosage has averaged about 50 millicuries divided into 2 or 3 weekly administrations in water by mouth an average of 5 to 6 weeks elapsing before noticeable relief accompanying a drop of basal metabolic rate which is kept from descending too far by small amounts of thyroid

Of prime import is the fact that in many cases there slowly, but spontaneously develops an adequate collateral coronary circulation and while that is going on nitrites in particular nitroglycerine (0 3 to 0 6 mg or 1/200 to 1/100 gr) and erythrol tetranitrate (15 to 30 mg or ¼ to ½ gr) may be used often very effectively prophylactically as needed or regularly to tide over many weeks or months of trouble during which care should be exercised to avoid undue strain physical or emotional I have found this procedure often the best of all

For the immediate therapy of angina pectoris the nitrites are most useful for congestive failure as evidenced by dyspnea or edema (pulmonary or systemic) digitalis and diuretics (see Chapter 30) for coronary thrombosis with myocardial infarction and cardiac asthma morphine and if there is not adequate relief thereby a trial of oxygen by inhalation or of aminophyllin by vein, for ventricular paroxysmal tachycardia quinidine and for atrial fibrillation digitalis or quinidine In the case of coronary thrombosis it may be necessary to give large amounts of morphine even intravenously to control the pain often as much as ½ to 1 gr in divided doses in the course of a few hours or caffeine for collapse It is wise however to give no more morphine or its derivatives than is absolutely necessary because of the nausea the strain of vomiting constipation and the depression that commonly result If morphine does not in some cases control the very prolonged pain of myocardial infarction it is reasonable to try the effect of oxygen inhalation or of aminophyllin intravenously or of papaverine (0 2 gm 3 gr by mouth or 0 1 gm 1½ gr intramuscularly) these measures are usually disappointing but sometimes they help A ration of 0 2 gm (3 gr) of quinidine sulfate every 4 to 6 hours during the first 2 weeks of acute myocardial infarction or in cases of angina pectoris decubitus may prevent ventricular tachycardia and fibrillation it should be used routinely as a measure to reduce mortality in coronary heart disease (Borg 1939)

All of the various nitrites act by their vasodilating effect either directly to improve the coronary circulation by increasing its volume or indirectly by decreasing peripheral arterial resistance to relieve the work of the heart or more probably by both of these actions The most potent and rapid in effect of all the nitrites is the volatile *amyl nitrite* introduced by Brunton in 1867 It is inhaled from a small glass container (pearl or ampoule) broken at the

moment it is needed usually the amount in each container is 2 or 3 minims (0 12 to 0 18 cc) Inhalation causes in a few seconds flushing of the face pounding of the pulse in the head and all over the body and relief of the angina pectoris if inhalation is long continued dizziness and a disagreeable headache may result *Nitroglycerine* (glyceryl trinitrate glonoin or trinitrin) introduced by Murrell in 1879 is after amyl nitrite the next most rapidly potent nitrite being absorbed in a minute or two with relief of angina pectoris and with the production of symptoms and signs of vasodilatation it is best taken in the form of a quickly soluble tablet containing 1/200 gr (0 0003 gm) of nitro glycerine crushed and held in the mouth for rapid absorption it must be reasonably soft fresh and potent for sometimes the tablets are hard or become old and relatively inert If the dose of 1/200 gr is ineffective 1/100 gr may be used but it is better to try first the smaller dose in any given case since it is often sufficient and does not produce so many disagreeable reactions—flushing headache pounding pulse faintness and even syncope—to which some persons are subject even smaller doses 1/400 gr (0 00015 gm) or less are sometimes adequate especially for prophylactic use (see below)

Nitroglycerine is in most respects preferable to amyl nitrite in the treatment of an attack of angina pectoris for it is easier to carry and to use (not requiring the breaking of a glass container) is effective enough without being disagree ably and unnecessarily potent and its lower cost favors its constant use when needed rather than its reservation for rare occasions Less important is *sodium nitrite* introduced by Hay in 1883 which in the dose of ½ to 1 gr (0 03 to 0 06 gm) in tablet form by mouth is rather slow in its effect requiring five to ten minutes but has the advantage of a longer continued effect (an hour or more) hence it can be used somewhat in a prophylactic way For immediate therapy it is far inferior to nitroglycerine and amyl nitrite its actual effect is however similar Next comes *erythrol tetranitrate* introduced by Bradbury in 1895 taken in ¼ to ½ gr (0 015 to 0 03 gm) doses in tablet form by mouth it is more valuable than sodium nitrite because its effect lasts for several hours it is very slow in its action taking fifteen to thirty minutes to produce the usual nitrite effect *Mannitol hexanitrate* introduced by Bradbury in 1895 and *mannitol pentanitrate* introduced by Marshall and Wigner in 1902 rarely used in the past have been recently revived they are taken in 1 gr (0 06 gm) doses in tablet form are very slow in their action requiring one hour to pro duce full effect but they continue to be effective for five or six hours Finally *octyl nitrite* a liquid less volatile and effective than amyl nitrite has recently been introduced rather to be used prophylactically than in the direct treat ment of an attack of angina pectoris administered by inhalation it requires 30 seconds for its effect which lasts about 20 minutes it has not established itself as at all preferable to the nitrites already in use The last nitrites men tioned are primarily for prophylactic use erythrol tetranitrate being preferable although expensive and likely to give rise as are also the other preparations to obstinate and disagreeable headaches The following table summarizes the speed and duration of action of the various nitrites

Table 10

THE SPEED AND DURATION OF ACTION OF VARIOUS NITRITE DRUGS

Preparation	*Speed of action*	*Duration of effect*
Amyl nitrite	A few seconds (10)	A few minutes (10)
Octyl nitrite	30 seconds	20 minutes
Nitroglycerine	1 to 2 minutes	30 minutes
Sodium nitrite	5 to 10 minutes	1 to 2 hours
Erythrol tetranitrate	15 minutes	3 to 4 hours
Mannitol hexanitrate or pentanitrate	30 minutes	4 to 5 hours

The most effective drug after the nitrites is *alcohol* it was used routinely one hundred years ago before the introduction of the nitrites and even now when the nitrites are not available an ounce or two of whisky brandy or rum may give quite rapid relief from angina pectoris usually in the course of a very few minutes However inasmuch as a paroxysm of angina pectoris is likely to subside before alcohol exerts its full effect these various beverages are more useful in prevention than in treatment and inasmuch as alcoholism as a habit may be established by this procedure the prophylactic use of nitroglycerine is much to be preferred It should be added that although heavy drinkers seem to show little atheroma the moderate or even the considerable use of alcohol does not protect against coronary heart disease in middle age I have encountered a good many patients who have proved this point.

Other drugs for the immediate treatment of angina pectoris are either less effective than the nitrites and alcohol or inadvisable Ether and chloroform were sometimes used in treatment in place of alcohol in the early days before the introduction of the nitrites but now there is little place for them they may be effective in severe prolonged attacks Bromides are of little use except to calm nervous excitement Morphine is too slow in its action and is far less effective than the nitrites it should be avoided in the vast majority of cases and simply reserved for severe long continued pain not relieved by an effective nitrite and generally due to myocardial infarction Serious drug addiction and psychoneuroses have frequently followed the unwise use of opiates in the treatment of angina pectoris Digitalis and strophanthin do not relieve angina *pectoris in fact they may aggravate it but they can be used* without fear to relieve congestive heart failure or to control the ventricular rate of atrial fibrillation in spite of the presence of attacks of angina pectoris

Diet Much has been said and written about the relationship of diet to coronary atherosclerosis (the basis of 99 per cent of coronary heart disease) but most of it is still conjecture and opinion It is certainly true that the deposition of cholesterol in the coronary arterial intima is the fault with which we are concerned that cholesterol foods are richly ingested in this country and that coronary patients and candidates are prone to have high cholesterol contents in their blood But as stated earlier in this chapter under Etiology doubtless much if not the major part of this blood cholesterol is

of endogenous origin associated with metabolic processes and not exogenous The total calories of a rich diet may well be most important of all

In the present state of our knowledge it would seem wise to maintain a diet of moderation low in cholesterol foods (especially eggs butter cream and cheese) in robust persons with coronary heart disease or who look like candidates It probably is not necessary or wise to exclude these fats completely but it does appear advisable to treat obesity to recommend limited caloric intake (according to activity) to avoid large or rich meals and perhaps to limit also heavy use of tobacco Alcoholic beverages may be permitted provided their caloric values are taken into consideration but they do not have any special virtues

Control of various activities care of bowels and sometimes hospital or sanitarium treatment are necessary in the therapy of coronary heart disease and its complications Much attention may be needed in a chronic case to prevent the occurrence or recurrence of serious complications but each patient must be considered individually on each occasion and not be made to follow any set rules It need only be said that any activity or strain of doubtful effect should be avoided unless the patient is thereby too depressed o unhappy A balance must always be sought between too much and too little restriction of life not only from the standpoint of longevity but also from that of happiness

Acute coronary thrombosis must be regarded more seriously than most cardiac conditions and careful rest for weeks or months (a minimum of three to four weeks) should be prescribed in order to assure as sound a healing of the myocardial infarct as possible with a very gradual and careful convalescence (a minimum of one month after completing the rest period) by wise treatment at the start life may doubtless be prolonged for many years in some cases At times shortly after coronary thrombosis when the patient is feeling well and therefore possibly too active sudden death from cardiac rupture or other cause may occur sometimes however this accident is not preventable Sutton and Davis (1931) made the interesting observation that in dogs rest for six days after the production of cardiac infarction permitted the formation of a small well-contracted scar without thinning of the wall of the ventricle while exercise within three days of the infarction produced aneurysmal bulging of the ventricular wall with a thin scar The absolute need of complete rest for two weeks after a large acute myocardial infarction in man has been clearly demonstrated by the finding of rupture of the heart during the first twelve days in 16 or 73 per cent of 22 psychopathic patients in contrast to only 10 cases or 9 5 per cent of 105 patients in the wards of a general hospital (Jetter and White 1944 Friedman and White 1944)

As the result of experience during the last twenty five years I have found that a very satisfactory plan of treatment for the average case of acute myocardial infarction is one month of full rest (the first fortnight very quiet to avoid so far as possible serious complications in particular dilatation and rupture of the heart during the critical period of softening of the wall and the beginning of the laying down of the scar) one month of gradually increasing

activity (the first week in a chair a little more each day the second week walking on the level increasing distances the third week going slowly over the stairs once a day and the fourth week going out for short daily rides weather permitting) and a third month if possible (although this is not always essential) to consolidate the recovery nervously as well as otherwise One may need to lengthen or shorten these three periods of the convalescence as circumstances demand It is of importance to realize that the heart may recover more rapidly than the depressed mental state which is so often a complication Too long a stay in bed or too long a total convalescence is bad for the morale and the general health During the last two decades the pendulum has swung from one extreme to the other with respect to the length of time at full rest and of total convalescence from two or three months of the former and six months to a year of the latter to a few days only at rest and a few weeks only away from work The wisest course is doubtless to avoid both these extremes

An important consideration in the treatment of acute myocardial infarction which has been much debated is that of bed rest versus rest in a chair In mild cases with small infarcts there is no reason why the patient may not sit in a comfortable chair by the bedside even during the first week avoiding *however physical exertion Also if a patient is very ill and has orthopnea* or otherwise is uncomfortable recumbent he may be lifted into a suitable large chair or better still use a chair bed (see Chapter 30) In any case a bedside commode for bowel movements is for many persons better than a bedpan since its use is much less of a strain Bathroom privileges are best reserved until after the first fortnight And finally quiet exercise of the legs daily while still otherwise at full rest is advisable to help prevent leg vein thrombosis

A limited diet to maintain a low basal metabolic rate during the process of healing of the infarct has been advised also (Master et al 1935) but this in extreme degree is usually unnecessary and probably at times unwise A light mixed diet of 1 800 to 2 100 calories in 4 or 5 small meals a day is a good plan In the case of an obese patient a low calorie diet is in order, and if congestion threatens the diet should be low in sodium

Other measures In recent years several new measures of treatment have been introduced to control certain manifestations or complications of coronary heart disease Paravertebral alcohol injections of the sympathetic nerve connections to the heart have been largely supplanted by sympathectomy itself but this procedure too is now rarely indicated in part because of the reversibility of the coronary heart disease in time in the majority of cases even of severe angina pectoris (including the decubitus type) by patience and medical therapy in particular free use of the nitrites often tiding over the disagreeable and hazardous period of serious illness and in part because of the superiority of irradiated iodine therapy (mentioned above) in the most obstinate cases The principle of total thyroidectomy ingeniously introduced in 1933 and soon abandoned has been recently revived as the medical measure just referred to Much direct surgery on the heart has been attempted to bring new blood supply by constructing anastomoses to the coronary circulation Beck has

been a leader in this field (1935 and since) and although many of the results have been disappointing especially in establishing pericardial adhesions (also produced via the omentum by O Shaughnessy 1937 and via powdered sub stances) new trials are in progress consisting most recently of grafting a systemic (e g brachial) vein into the coronary sinus and later on, partially occluding the sinus Fauteux (1941 1946 and 1948) performed much original work on the heart to improve the coronary circulation by ligating the great cardiac vein and to reduce the hazard of ventricular fibrillation by coronary neurectomy but these procedures though promising are still hazard ous in man

Anticoagulants both heparin and dicoumarin but especially the latter have been in the last decade introduced in coronary heart disease for two purposes Complications of thrombosis and embolism both pulmonary (chiefly from leg vein clots) and systemic from intracardiac thrombi mostly over a healing infarct have been distinctly diminished by anticoagulant therapy begun at the earliest stage of acute coronary thrombosis with myocardial infarction With or without initial heparin (which may prove wise if readily available) Di cumarol is given the first day usually in the dosage of 200 mg after a test of the prothrombin time has shown no abnormal delay and provided daily tests of the prothrombin time of the patient s serum can be accurately determined A daily dosage of 50 to 100 mg or none at all is given thereafter during the next three or four weeks to maintain a prothrombin concentration of 20 to 50 per cent of the normal Wright not long ago (1948) analyzed 800 cases of acute myocardial infarction half of whom received Dicumarol and half ob served as controls the mortality was 13 per cent in the treated patients and 23 per cent in the controls and there were thrombo embolic complications in only 13 1 per cent of the treated cases in contrast to 41 8 per cent of the controls A new oral anticoagulant more rapidly acting than Dicumarol called Tromexan is now on trial (Wright 1951)

Less amenable to proof the other purpose for anticoagulant therapy in coronary heart disease has been to prevent or delay coronary thrombosis itself This is still in the experimental stage and may prove to be both impractical and ineffective It may have to be continued for years and during its use the blood must be tested frequently (daily or every few days) to be safe for the hazard of hemorrhage exists as well as of ineffective dosage To combat serious effects of anticoagulants certain measures have been introduced the most effective is vitamin K_1 oxide (0 5 gm or more intravenously) whole blood transfusions have yielded minor temporary benefit (James et al 1948) As a matter of fact, vitamin K has even been recommended in the treatment of coronary disease in certain cases with the idea of preventing hemorrhage in the coronary wall (Doles 1947) but confirmation of this is still lacking

Last but not least one must treat the state of shock which not rarely com plicates acute coronary thrombosis or acute myocardial infarction Simple measures of absolute rest and quiet and nursing care with strong coffee by mouth and aminophyllin intravenously may suffice in mild cases but in serious shock

something radical may be needed to save a life Here transfusion with care under close observation may be helpful—up to 250 or 300 or more cc slowly given watching carefully for overloading of the veins pulmonary and systemic in the face of a weak heart muscle Plasma may be given instead of whole blood

Finally in all the therapy of coronary heart disease one must not lose sight of the very important facts (1) that the heart itself possesses a striking re cuperative capacity no matter what is done but (2) that great care in all details of physical activity and nervous strain in exposure to weather and in eating and other habits may be essential for survival over periods of acute or subacute trouble

Differential diagnosis Chronic coronary heart disease is often very difficult to discover and in the stage of congestive failure with arrhythmia may be hard to distinguish from rheumatic heart disease or thyrotoxic effects The age of the patient a history of angina pectoris the usual absence of characteristic murmurs of chronic valvular disease the usual absence of much cardiac en largement the finding of tortuosity of the aorta by roentgen ray and of intra-ventricular block or other even more specific coronary electrocardio-graphic patterns help to establish the correct diagnosis Myxedema too has been occasionally confused with coronary heart disease on the basis of the electrocardiograms which with abnormal *T* waves and low voltage of the *QRS* waves may be indistinguishable in the two chronic diseases, however, the appearance and symptoms of the patient readily reveal the myxedema con firmed by the very low basal metabolic rate These diseases may coexist.

Acute coronary occlusion with cardiac infarction has been frequently con fused in the past with *acute abdominal disease* such as acute indigestion gall stones and perforated peptic ulcer and laparotomy has been done in some cases by mistake Although position of the pain fever leukocytosis and gastrointestinal symptoms like vomiting may be common to the two conditions there are usually enough differences to make the distinction fairly certain The most important point in this differentiation is the past history in the one case *a story of angina pectoris or other cardiac symptoms or signs* and in the other a record of indigestion or colic Other signs and symptoms of importance in differentiating coronary thrombosis and acute abdominal disease are first to be found in the cardiac examination which may show characteristic abnormalities namely dilatation poor sounds pericardial friction rub and specific electro-cardiographic findings such as *T* wave changes and intraventricular or atrio-ventricular block Secondly the abdominal examination may show masses definitely localized tenderness or spasm or there may be jaundice or bleeding from the gastrointestinal tract Thirdly the pain in myocardial infarction is more often high under the sternum or both substernal and epigastric rarely epigastric alone and is very frequently referred to the arms especially the left And fourthly the victims of coronary thrombosis are preponderantly elderly or middle aged men while acute abdominal disease is common in middle aged women as well as in men Despite the greatest care however if

a diseased gallbladder is unusually high in position acting almost like an intrathoracic organ it may be mistaken for an infarcted heart in the presence of some coincident coronary heart disease

There are four other conditions that are especially likely to be confused with acute coronary occlusion they are acute pericarditis dissecting aortic aneurysm pulmonary embolism and mediastinal emphysema The first *pericarditis* is commonly misinterpreted particularly in young adults in whom the error can be serious both from the standpoint of prognosis and from that of treatment and of the plan of life the differentiation is as a rule easy in two particulars precordial pain that is felt preponderantly or only on respiration and little if at all when the breath is held is due as a rule to acute pleuropericarditis and not to myocardial infarction and an electrocardiogram that shows very little or very transient or unusual abnormalities (such as transient elevation of the *S T* segments or flattening or inversion of the *T* waves in all leads) points much more to pericarditis than to myocardial infarction The youth of the patient is often a clue but the severe long continued pain fever, leukocytosis and pericardial friction rub may easily lead one astray *Dissection of the aortic wall* is to be distinguished by the very abrupt onset of most severe pain (not working up to a crescendo as in most cases of coronary thrombosis) the reference of the pain almost invariably to the back and often down to the legs the evidence of obstructed circulation in the branches of the aorta especially the iliac and femoral arteries the relatively normal electrocardiogram and the almost constant presence of chronic hypertension In the case of *pulmonary embolism* there is usually a story of recent surgical operation or injury association with thrombophlebitis more often severe dyspnea or prostration than severe pain and normal or characteristic electrocardiogram (if the acute cor pulmonale is present) (see Chapter 20) the chief difficulty with respect to this particular differential diagnosis is that both conditions not rarely occur together in the same patient one leading to the other *Mediastinal emphysema* (Hamman 1937) is fortunately very rare but it may be very confusing and give rise temporarily (that is for a few hours) to symptoms and signs that simulate acute myocardial infarction there may be intense substernal pain and a state bordering on shock the heart sounds may be weakened or attended by crepitations which might casually be confused with friction there may be a temporary change in the electrocardiogram and slight fever and leukocytosis but the differentiation should not be difficult if this condition is borne in mind because of the rapid clearing of the signs and symptoms and the usual finding of air in the mediastinum or even under the skin

Besides these five conditions with which acute coronary occlusion may readily be confused there are many other diseases which may more or less uncommonly be mistaken for it Herrick (1935) listed 28 different conditions which he had himself seen mistaken for coronary thrombosis they are as follows paroxysmal angina pectoris cardiac arrhythmia cardiac neurosis neurocirculatory asthenia malingering acute pericarditis syphilitic aortitis with and without aneurysm dissecting aortic aneurysm pleurisy pneumonia

carcinoma of bronchus and lung massive collapse of the lung pneumothorax pulmonary embolism herpes zoster, arthritis of costochondral articulation shoulders and spine bursitis gallstones peptic ulcer, carcinoma of stomach or duodenum acute gastritis spastic colitis diaphragmatic hernia tabetic crisis and impending diabetic coma Diaphragmatic flutter might be added to this list

Finally angina pectoris as a symptom of coronary heart disease may likewise be overdiagnosed most commonly when there is indigestion with cardiospasm (with or without a hiatus or diaphragmatic hernia), neurocirculatory asthenia or cardiac arrhythmia Angina pectoris as a characteristic symptom of coronary insufficiency due primarily to coronary atherosclerosis has been well described earlier in this chapter especially in the quotation from Heberden It is closely simulated only by spasm of esophagus or cardia of stomach (cardiospasm) from which it is to be as a rule readily distinguished by its relationship to effort rather than eating and by its more rapid response to nitroglycerine

If in rare cases who are not gravely ill there is serious doubt about the diagnosis of coronary insufficiency recourse may be made to exercise tests such as customary walking or stair-climbing or Master s two-step test or to Levy s anoxemia test

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CHAPTER 22

NEUROCIRCULATORY ASTHENIA (DA COSTA'S SYNDROME, ALSO CALLED "THE SOLDIER'S HEART," "EFFORT SYNDROME," AND ANXIETY NEUROSIS) CARDIAC NEUROSIS AND PSYCHOSIS

NEUROCIRCULATORY ASTHENIA

Introduction Despite considerable research on this mysterious malady since the last edition of this book and the elucidation of certain of its aspects the fundamental mechanism still eludes us and we have as yet no specific therapy The chapter therefore requires relatively slight changes

Neurocirculatory asthenia also called less adequately the soldier s heart effort syndrome and the anxiety neurosis is an important condition of instability and abnormal irritability of the nervous and circulatory systems of unknown cause It tends to be precipitated as an acute disorder in many persons by physical exhaustion nervous strain and infections and so constitutes a kind of fatigue syndrome, in some individuals however who appear to be constitutionally inadequate it is a more or less chronic condition, usually associated with or a part of, a psychoneurosis of the anxiety type It is not in itself disease of either heart or nervous system but a functional circulatory and nervous disorder often confused or associated with heart disease hence it forms an essential part of this book

In the present state of our knowledge, and until the problem is solved I would suggest the following definition *Neurocirculatory asthenia is a condition of ill health characterized by a group of symptoms consisting of dyspnea (often with sighing respiration) palpitation exhaustion precordial pain (most often an ache) dizziness nervousness and sometimes tremor sweating headache and syncope aggravated by effort or excitement and attending or following anxiety neuroses infections or physical or nervous strains especially in hypersensitive individuals who in extreme cases may show the condition more or less constantly with little or no provocation* That such a

state of ill health exists there can be no doubt no matter what its pathogenesis or exciting factors Until we can give it a fundamentally better designation the descriptive term neurocirculatory asthenia seems still to be the best It is neither fatigue per se nor infection nor thyrotoxicosis nor nervous strain nor psychoneurosis it is a state of ill health which may attend or follow any of these conditions or indeed others too or even frequently stand alone

Physical effort of extreme degree will always produce symptoms of circulatory distress but fatigue of skeletal muscles or of nervous system may prevent such effort The symptoms of circulatory distress are dyspnea palpitation and precordial or substernal oppression alone or combined Generally associated with them are weakness and often dizziness faintness and tremor The combination of these symptoms occasioned by exertion has been called the effort syndrome Such effort syndrome may be induced easily in weak tired sick or nervous persons and with difficulty in strong well trained and calm individuals whether heart disease is present or not Even a perfectly normal person if sufficiently strenuous will show the syndrome in some form perhaps having dyspnea alone palpitation substernal or precordial oppression or two or three of these symptoms together It is likely that under such circumstances in *normal* persons the relative abilities of the myocardium to maintain the general circulation and of the coronary circulation to maintain the myocardium determine whether dyspnea or pain will be the predominant symptom in most normal persons dyspnea will be preponderant but even in normal persons a third factor besides myocardial and coronary reserves namely nervous sensitivity must be taken into account as modifying symptoms or exaggerating one or another especially precordial pain palpitation or faintness *Hypersensitive* individuals in whom the effort syndrome is easily induced are likely to develop the same symptoms on excitement as on exertion at such times the symptoms form an excitement syndrome and not an effort syndrome

The effort syndrome though easily induced might be considered at first thought to be unworthy of any special discussion since so far as we know it is not an organic disease and since it may occur in perfectly normal persons but when it is of high degree that is when it is very easily induced and the symptoms are marked it is important for three reasons In the first place it is itself often a partially or completely incapacitating condition Secondly proper treatment is very important and is often neglected And thirdly it is essential to distinguish it from organic heart disease or to recognize its presence when it complicates organic heart disease

An abnormally high degree of effort syndrome has long been recognized generally as but a part of a neurasthenic state and it has so been labeled in medical practice Occurring with great frequency among the British soldiers in India and among the Union soldiers during the American Civil War as the result of excessive strain and hardship it was called the excitable or irritable heart of soldiers (Myers 1870 DaCosta 1871) DaCosta s classical account is the first good description of the condition and so deserves quotation here

DaCosta J M On Irritable Heart a Clinical Study of a Functional Cardiac Disorder and Its Consequences *Am J M Sc* 1871 LXI 17

'In this paper I propose to consider a form of cardiac malady common among soldiers but the study of which is equally interesting to the civil practitioner on account of its intimate bearing on some obscure or doubtful points of pathology Much of what I am about to say I could duplicate from the experience of private practice yet I prefer to let this inquiry remain as it was originally conducted on soldiers during our late war The observations here collected were made on a series of upwards of three hundred cases

General Clinical History—The general clinical history of many of the cases was this —

"A man who had been for some months or longer in active service would be seized with diarrhoea annoying yet not severe enough to keep him out of the field or attacked with diarrhoea or fever he rejoined after a short stay in hospital his command and again underwent the exertions of a soldier's life He soon noticed that he could not bear them as formerly he got out of breath could not keep up with his comrades was annoyed with dizziness and palpitation and with pain in the chest his accoutrements oppressed him and all this though he appeared well and healthy Seeking advice from the surgeon of the regiment, it was decided that he was unfit for duty and he was sent to a hospital where his persistently quick acting heart confirmed his story though he looked like a man in sound condition Any digestive disturbance which might have existed gradually passed away but the irritability of the heart remained and only very slowly did the excited organ return to its natural condition Or it failed to do so notwithstanding the use of remedies which control the circulation thus the case might go on for a long time and the patient after having been the round of hospitals would be discharged or as unfit for active duty placed in the Invalid Corps

Causes—In discussing the causes we are led to examine some of the most interesting questions connected with this inquiry But in no part of it is it more difficult to arrive at fixed conclusions for many causes seem at times to have combined and it is scarcely possible even by the most rigorous analysis to fix specially upon one In the subjoined table great care has been exercised to arrive at the probable causing element The cases which have served as its basis have been only so far selected that doubtful or ill marked ones have been excluded and that those patients who were chosen were for the most part in good general health

Analysis of 200 Cases

Fevers	34	17 per cent
Diarrhoea	61	30 5 per cent
Hard field service particularly excessive marching	69	34 5 per cent
Wounds injuries rheumatism scurvy ordinary duties of soldier life and doubtful causes	36	18 per cent
	200	100

But in looking further and in endeavouring to explain the *nature of the malady* there is room for much doubt and difference of opinion

Treatment The treatment is never a short one and the question arises, would it not be better for the government at once to discharge these heart cases? I think not The very worst ones those which after some months of treatment show

no decided improvement had better be discharged Until I understood the malady I retained the patients a long period in the hospital later in the war a short time sufficed to make the proper disposition of them

" And from a military point of view further it enforces the lessons how important it is not to send back soldiers just convalescent from fevers or other acute maladies too soon to active work that recruits especially very young ones be as far as practicable exercised and trained in marches and accustomed to fatigue before they are called upon to undergo the wear and tear of actual warfare and it exhibits some of the dangers incident to the rapid and incessant manoeuvring of troops

Rediscovered as a common military disorder in World War I this state of ill health was called the soldier s heart disordered action of the heart and later effort syndrome The term neurocirculatory asthenia was finally employed in this country (Oppenheimer and associates 1918) and this remains at the present time the most satisfactory designation because it expresses its abnormal character by referring to both neurasthenic state and circulatory symptoms and at the same time it does not limit the term to effort or irritability or soldier or make it too general by calling it by the vague inclusive designation cardiac neurosis It is simply one type of cardiac neurosis or of irritability of the heart it occurs in civilians as well as in soldiers it results from excitement as well as from effort and it is not a normal response to ordinary effort Also its symptoms are not exactly like those produced by effort in a normal healthy person

Frequency It is impossible to state accurately the frequency of neurocirculatory asthenia for several reasons The borderline is very wide and indistinct and where the normal response ends and the abnormal response begins especially with such variable factors as human individuals it is impossible to say Moreover a normal person may have the condition for a short time during or after an acute illness or especial fatigue without its being particularly noted by patient or doctor And finally it has been included by most practicing physicians as a part of the more general terms neurasthenia nervous prostration and neurosis

It is possible however to estimate roughly its frequency when well marked Although common enough in civilian life it is far less frequent and less severe than in the army in wartime Lewis (1940) stated that during World War I sickness imputed by medical officers of the British Army to disturbances of the cardiovascular system was a chief malady one such case being numbered for every four cases of wound following chest complaints as the second largest group of medical ailments Five out of six of those cardiac cases suffered from neurocirculatory asthenia After the World War of 1914–1918 there were 44 000 British soldiers who were pensioned for neurocirculatory asthenia In World War II the condition cropped up in prominent degree in only the most strenuous campaigns but in mild form it was encountered in many psychoneurotic soldiers undergoing their training in camps at home

Of a series of 3 000 civilian patients with cardiac symptoms or signs who sought medical advice both in hospital and in private practice in New England (White and Jones, 1928) 302 or 10 per cent were found to have neurocirculatory asthenia alone and 62 or 2 per cent more showed well marked neurocirculatory asthenia complicating organic heart disease over half of such disease being of rheumatic type and another quarter of hypertensive type Nearly 3 per cent of 2 314 cases of organic heart disease showed definite neurocirculatory asthenia A more recent analysis of 5,000 private patients with cardiac symptoms or signs seen by myself has revealed 687 (13 7 per cent) with definite neurocirculatory asthenia 448 (65 2 per cent) of these were uncomplicated by organic heart disease 135 (19 6 per cent) were so complicated and in the remainder (104 or 15 2 per cent) there was doubt about the presence of organic heart disease Among the cases of organic heart disease found with neurocirculatory asthenia (a total of 4 7 per cent of the organic heart cases) rheumatic heart disease was most frequent (44 4 per cent) coronary heart disease was second (21 4 per cent) and hypertensive heart disease was third (18 per cent), there was only one case of cardiovascular syphilis

The victims of the disorder are physically unfit as it were chronically out of condition unable to maintain any degree of physical effort and quickly accumulating respiratory inefficiency and an excess of lactic acid on exercise

Etiology *Cause* The cause of neurocirculatory asthenia is not known The symptoms suggest that it may be a disorder of the autonomic or vegetative nervous system a true neurosis not necessarily a psychoneurosis but, even if it is we are as yet unaware of its pathogenesis The fundamental origin of the irritability and fatigability of the nervous system in so-called neurasthenia is still obscure these have usually been called functional disorders but the mechanism of such disorders is as yet unexplained Abnormalities of central nerve cells induced by fatigue in experimental animals have been noted and may be possible factors Moreover why gastrointestinal symptoms are most prominent in some neurasthenic patients cerebral symptoms in others and cardiovascular (neurocirculatory asthenia) in others has not been explained variations in innervation or early accidental association with other troubles (indigestion headache extrasystoles or cardiovascular symptoms on exertion) may be the answer We can only say now that in some patients neurasthenia manifests itself preponderantly by circulatory symptoms and that neurasthenia itself is a disorder commonly found in certain individuals usually under especial strain who are equipped with a particularly sensitive nervous system

Age *Neurocirculatory asthenia is commonest in young adults* but it may occur at any age after early childhood it appears to be very rare in young children and it tends to decrease in incidence after early adult life Of the 365 cases of this condition in White and Jones series over half were between twenty and forty years old 23 9 per cent being in the third and 27 4 per cent in the fourth decade of life In the second decade 7 4 per cent were found

After the age of fifty years there were still a moderate number of cases—15 3 per cent In war time among the soldiers the great majority of cases were found in the third and fourth decades doubtless because such age groups made up the bulk of the soldiers

Sex Females are affected more often than males The ratio in the series of White and Jones was 59 per cent female to 41 per cent male

Heredity One of the most fundamental etiologic factors is that of heredity It is common to find that the close relatives and recent ancestors of patients with neurocirculatory asthenia have also had sensitive nervous systems having suffered perhaps from this very same condition in the course of nervous prostration or other such trouble Recent studies have suggested that neurocirculatory asthenia belongs to the Mendelian dominant group of inherited disorders (Wheeler et al 1948)

Strain Besides heredity the one other etiologic factor of greatest importance is that of strain This may be the result of worry over business social or family troubles emotional conflicts physical or nervous fatigue or both (as in the war) insomnia exhaustion from acute infection or other illness or undernourishment

The toxic effect of tobacco alcohol tea coffee and other substances does not itself cause neurocirculatory asthenia although it may aggravate or perhaps even precipitate it During World War I (1914–1918) it was thought that overindulgence in these things particularly in tobacco and alcohol might explain the great frequency of neurocirculatory asthenia but actually the reverse was found namely that the victims of this disorder realizing their sensitiveness indulged in these things less than did the average soldier for otherwise their symptoms were often aggravated

Other possible fundamental causes of neurocirculatory asthenia that have been suggested during the past 25 years are thyrotoxicosis low grade active infection adrenal hyperactivity hyperventilation resulting in alkalosis and salt lack but none of these possible factors have been confirmed All these conditions may precipitate or aggravate the symptoms of neurocirculatory asthenia but they do not seem to be the fundamental cause Hyperventilation combined with an anxiety neurosis is the nearest approach to the answer to date the neurosis causing in some unknown way a sighing respiration with hyperventilation the latter inducing in its turn faintness dizziness palpitation and precordial discomfort

Pathology There are no known pathologic changes in neurocirculatory asthenia The heart as a rule is structurally normal although there is sometimes associated organic disease No lesions of the nerves or of the glands of internal secretion have been found

Symptoms The symptoms of neurocirculatory asthenia are usually like those of effort syndrome in normal persons In cases with lesser degrees of neurocirculatory asthenia the symptoms are not only relatively mild but they are fewer in number and in only the pronounced cases are all the classical symptoms present—dyspnea palpitation precordial pain and tenderness

faintness dizziness tremor, sweating and nervousness In a series of 100 cases of neurocirculatory asthenia the four cardinal symptoms namely palpitation respiratory discomfort precordial pains or aches and exhaustion were of almost the same frequency varying in the order named from 78 to 73 per cent (Craig and White 1934)

The dyspnea is mostly subjective there being an unpleasant consciousness of the ordinary respiratory act without much of any evident labor distress or rapidity of respiration (a breathing trouble often in spells) sometimes there is a tachypnea and during World War I cases were noted with an extreme but temporary acceleration of respiratory rate even to 100 or more per minute *An interesting and commonly associated phenomenon is the abnormal increase of a tendency to sigh* In fact the presence of abnormally frequent sighing is a helpful sign of the existence of neurocirculatory asthenia as differentiated from organic heart disease for heart disease even in the presence of heart failure is rarely attended by sighing unless it is complicated by neurocirculatory asthenia

The palpitation is for the most part simply the keen consciousness of the forceful action of the heart beating regularly and often rather rapidly arrhythmia is uncommon but if premature beats or paroxysms of tachycardia do appear they usually aggravate the condition considerably and sometimes they set it off

The precordial pain is as a rule a dull or heavy ache in the left breast, lasting for hours and not radiating but occasionally it is interspersed with sharp stabbing sensations substernal oppression is unusual though neurocirculatory asthenia may and in fact frequently does complicate angina pectoris When the heartache or infrequently the substernal ache is severe it may radiate to the left arm and then be mistaken for angina pectoris still more easily Left breast tenderness is distinctive evidence of neurocirculatory asthenia

The fourth prominent symptom namely a feeling of exhaustion present almost all the time but especially noticeable the first thing in the morning is a striking characteristic in the great majority of cases of neurocirculatory asthenia Not rarely it is the outstanding symptom Other common symptoms —dizziness faintness and tremor—are present in varying degrees and indicate the instability of the nervous state and of the vasomotor control

It is usually the combination of excitement exertion and fatigue that precipitates the maximum degree of symptoms in a susceptible individual and it is this combination in war times that occasions the great exaggeration of the disorder in so many nervous young soldiers More or less incapacity results from marked neurocirculatory asthenia often more than that resulting from organic heart disease and sometimes even complete disability ensues It is a real and not an imaginary incapacity even though at first glance it may have appeared imaginary during World War I (1914–1918) when it was sometimes labeled "malingering and even though in civilian practice it has frequently been diagnosed as mere nervousness

An important finding in neurocirculatory asthenia of high degree or easily induced as in civilian life or in early milder training for war is the associated psychoneurosis of anxiety type So common is this that the two conditions have sometimes been confused one for the other or considered to be synonymous the term anxiety neurosis having come to mean for many the same collection of symptoms which identify neurocirculatory asthenia although strictly one can be neurotically anxious about something without dyspnea chest pain or palpitation Experience has shown however that one condition can occur without the other as well as that either one can excite the other Nevertheless the close correlation is helpful in the weeding out of the more pronounced cases of neurocirculatory asthenia from the recruits for the armed services by the neuropsychiatrist who is particularly trained to pick out the psychoneurotics and those likely to become such

Signs The signs of neurocirculatory asthenia are general the heart itself giving no evidence of trouble other than a tendency to increased force of action and sometimes increased rate unless of course it happens to be the seat of organic lesions A worried expression tremor sometimes flushing somewhat quickened respiration and sweating are commonly found in a well marked case Special methods of examination such as blood pressure studies roentgenology and electrocardiography reveal no particularly characteristic abnormalities in an occasional case however the *T* waves in Lead 2 of the electrocardiogram may be temporarily flattened or even inverted probably due either to a preponderant sympathetic nerve imbalance or to an unusually vertical position of the heart (so common in this type of individual of asthenic build) or to both these factors (see Chapters 2 and 9) The blood pressure may be a little elevated and variable Strength and endurance tests and vital capacity usually show a subnormal value and are considerably reduced in marked cases this fact weakens the value of such strength and vital capacity tests in judging the state of the heart itself An interesting abnormality is an easily induced oxygen debt on exercise with excess accumulation of lactic acid Another interesting finding is abnormality of shape of the capillary loops at the base of the nail in neurocirculatory asthenia (Cobb et al 1946) somewhat as has been noted in certain neurotic states

Course and prognosis The course of neurocirculatory asthenia is very variable but the prognosis is always good so far as length of life is concerned in fact better than the normal expectation (Wheeler et al 1950) The degree of incapacity depends on several factors chiefly on the intensity of the symptoms and on the adequacy of treatment Recovery from a considerable degree of neurocirculatory instability is possible with care but the patient is always likely to have a return of trouble if there is a return of the causative factors—infection fatigue worry and emotional stress If these factors cannot be controlled neither can the neurocirculatory asthenia be controlled. At the height of World War I it was suggested that this condition was but a forerunner of thyrotoxicosis or of heart disease or an accompaniment of infection but none of these prophecies was fulfilled

Of 558 soldiers with the condition reported by Lewis (1918) during World War I 286 (51 per cent) were found to be unfit for all military service and of the remaining 272, 38 had to be removed from service later In civilian life complete incapacity is much less for two reasons (1) the degree of neurocirculatory asthenia is as a rule less marked in civilians and (2) the strain of civilian life and work to which the patient must return is less than that of military service Nevertheless it must be recognized that more or less complete incapacity can occur even in ordinary civilian life However a follow up study of 173 cases of neurocirculatory asthenia who had been examined by myself for the first time over twenty years ago has shown that the majority are still able to live a useful and reasonably comfortable life (Wheeler Reed Cohen and White, 1950)

A series of 601 war veterans with neurocirculatory asthenia was studied over a period of five years by Grant (1925) to determine the immediate prognosis of the condition Of these cases 15 3 per cent recovered entirely 17 8 per cent improved 56 2 per cent remained stationary and only 3 2 per cent became worse the remainder became ill or died from other diseases The incidence of serious disease in the group was 8 7 per cent the most frequent infection was pulmonary tuberculosis (3 7 per cent) The incidence of definite heart disease was only 1 per cent The total deaths were but 14 (2 3 per cent)

So far as we know there is no tendency for patients with neurocirculatory asthenia either to die prematurely or to develop organic heart disease but they often do live considerably restricted lives

Complications There are no particular complications of neurocirculatory asthenia except the anxiety neurosis although the condition may itself complicate any other trouble such as infection heart disease chronic illness of other nature or trauma Sometimes the symptoms of neurocirculatory asthenia like other symptoms such as the palpitation resulting from paroxysmal tachycardia lead to anxiety about them and establish an anxiety neurosis and apparently vice versa thus a vicious circle is easily established and is often hard to break

Treatment If fatigue physical or nervous or infectious is primarily or even secondarily responsible for neurocirculatory asthenia rest is the important therapy for the moment and for as long—days weeks or months—as may be necessary adequately to counteract the fatigue The rest which may need at first to be complete should be followed as soon as possible by a program of rehabilitation re-education and retraining Reassurance at the start and in adequate doses afterward is often necessary but elaborate psychotherapy is generally not needed In fact since this condition is neither heart disease nor a mental disorder both cardiologist and psychiatrist are well kept away after the diagnosis has been established so that the patient may not develop unnecessary fears about either heart or mental state unless complications make the presence of such consultants advisable It is essential at the outset in cases of neurocirculatory asthenia to rule out exciting factors such as infection and important psychoneuroses that in themselves need treatment

One of the prime essentials in the treatment of neurocirculatory asthenia is to take the patient wholly into one s confidence to explain fully what the situation is so far as we know it and to dispel any fears of heart disease or death The condition must be discussed seriously not lightly as if it were of no importance It is just as wrong to regard the whole trouble as negligible or imaginary as is so often done as it is to regard it as a dangerous or serious state which may threaten life and which demands rest in bed Equally pernicious are the two extremes of diagnosis (1) myocarditis or cardiac insufficiency and (2) no disease or imaginary trouble A careless disregard of the disorder with hasty reassurance may make as much of a permanent cripple of the patient who perhaps consults the advice of charlatans for their sympathy after being rebuffed by the regular medical profession as does a grave face with the order to go to bed and to take digitalis A half hour or an hour spent in full explanation at the onset of trouble or at least at the first medical consultation and a clear outline of treatment may save many days weeks or even years of invalid existence and hundreds of dollars spent on all kinds of doctors and medicines So much good can be done in this way that too much emphasis cannot be placed on this method of procedure it is often more fruitful and may need more skill and understanding than the treatment of a dozen cases of true heart disease

The plan of life of the patient is to be worked out with care Usually normal but quiet work and play are to be advised with avoidance of late hours coffee tea overindulgence in alcohol and tobacco strenuous vacations excitement in general too many hours at work and new and burdensome tasks or duties Often the patient himself is aware of this necessity but he has perhaps disliked to humor his symptoms or to fall behind his fellows in strenuous living in the business professional and social world With clear medical advice however he realizes the wisdom of doing so and gradually he adjusts himself to suit his symptoms and is surprised at recapturing a feeling of well being After the preliminary talk a few further visits to the doctor may be all that are necessary to establish a satisfactory cure without the need of a single drug or a visit to some expensive sanitarium Symptomatic therapy for headache insomnia or extreme nervousness with bromides or hypnotics may be helpful but should be discontinued as soon as possible to avoid toxic effects and habituation Digitalis generally makes the condition worse by increasing the force of the heart action or by producing toxic symptoms like anorexia

Thus rest reassurance and re-education are the keynotes of the therapy but after the condition is well established and has been wrongly treated for several years it may be very resistant to improvement and some cases fail to respond to even the most enlightened treatment of the day

Attempts have been made at more or less specific therapy by attacks on certain conditions that have been thought to underlie or at least to accompany neurocirculatory asthenia but these measures have not proved of value or are still in the experimental stage they include denervation of the adrenal glands the administration of sodium chloride various vitamins and other

drugs and intensive psychotherapy We still await a specific cure for routine use

Differential diagnosis The three conditions from which neurocirculatory asthenia at first glance may be sometimes difficult to differentiate are true heart disease thyrotoxicosis and psychoneurosis The absence of cardiac enlargement of characteristic murmurs of valvular disease, of hypertension of signs of heart failure of angina pectoris, or of abnormalities of roentgen ray shadow and electrocardiogram indicates at once that heart disease is not responsible for symptoms or incapacity Before the valuable experience of World War I (1914–1918) young adults especially women with uncomplicated neurocirculatory asthenia were occasionally wrongly diagnosed mitral stenosis because of their forceful heart action and of the unfamiliarity of the medical profession with the syndrome of neurocirculatory asthenia, now such errors are rarely made

The absence of exophthalmos of thyroid gland enlargement and of abnormally high basal metabolic rate (carefully measured and judged) rules out thyrotoxicosis

The most difficult differentiation of all is between neurocirculatory asthenia and psychoneurosis particularly of the anxiety type This is true because of the frequency with which one is engrafted upon the other probably much as neurocirculatory asthenia is a common accompaniment of infection though the reverse is not true Since in the easily induced severer grades of neurocirculatory asthenia the anxiety neurosis is almost constantly found there is little or no point in differential diagnosis in this respect in such cases but in other patients more resistant to the condition it may be of considerable importance to distinguish the other exciting factors namely physical exhaustion nervous strain and infection from the anxiety neurosis itself It is probably best until we know more about it to regard neurocirculatory asthenia as a disorder of the autonomic or vegetative nervous system that is as a neurosis in contradistinction to a psychosis or psychoneurosis

The absence of fever or other evidences of infection indicates that neurocirculatory asthenia is not an immediate accompaniment of infection Finally the recent history of nervous strain fatigue or infectious disease in an individual with a sensitive nervous system helps to establish the diagnosis of neurocirculatory asthenia

PSYCHONEUROSES AND MENTAL DISORDERS

Any psychoneurotic state may have cardiovascular symptoms associated with it or be in part or completely based on a fear or a delusion of heart disease, even with no symptoms whatever This is very different from neurocirculatory asthenia where symptoms may be marked but where there may be no fear or delusion at all In some cases the two conditions may be combined as I have amply noted in the earlier part of this chapter

Heart symptoms or signs should be considered in their true light with relationship to the nervous disorder and specifically treated only if there is congestive failure angina pectoris or some such condition which can be definitely benefited such treatment if indicated may itself result in improvement of the nervous disease and reinforce psychiatric therapy

Mental disorders and nervous instability may be initiated or aggravated by the fatigue or poor cerebral circulation resulting from actual heart disease and failure generally in individuals in whom such mental or nervous trouble is rather easily induced in such cases satisfactory results from cardiac therapy so far as the heart and general circulation are concerned usually improve also the nervous and mental state but may not cure it Mental disorders and nervous instability that are brought to light by heart failure or by cerebral anoxia of other cause such as congenital heart disease with venoarterial shunt are simply latent troubles that tend to recur under other strains than heart failure and often progress to a permanent state of mental or nervous derangement A psychosis resulting from too much digitalis has been reported but not confirmed it is almost certain that such a psychosis is precipitated by faulty circulation rather than by the drug It is true however that sedative hypnotic and narcotic drugs given to cardiac patients may induce acute psychoses as they may in patients with other diseases or indeed in normal persons in such cases paraldehyde (2 to 3 drachms 8 to 12 cc, by mouth by rectum or intra muscularly to be repeated in three or four hours if necessary) is the best hypnotic though not infallible Acute psychoses have been temporarily induced in some patients rapidly dehydrated by vigorous diuresis

Hypochondriasis is a fairly frequent disorder and so far as the heart is concerned may be based on the occurrence or belief of the occurrence of heart disease in other members of the family or in friends with fear of development of similar trouble in the individual himself or on a slight symptom like palpi tation from a premature contraction or on mild neurocirculatory asthenia (effort syndrome) or finally on the knowledge of the possession of a *systolic* murmur which may be wholly unimportant It may be a very distressing con dition difficult to treat and requiring the aid of a psychiatrist or on the other hand it may be controlled easily by careful examination and reassurance

Hysteria may assume a cardiac phase without either symptoms or signs of cardiac nature After cardiovascular examination the treatment of the under lying psychiatric disorder should be turned over to expert hands

Schizophrenia (dementia praecox) may be associated or aggravated by heart disease as in a patient of my own with congenital patency of the ductus arteri osus of high degree with intense continuous machinery murmur and thrill who constantly reiterated her displeasure at having within her a woman who plotted against her with a roar of machinery Schizophrenia is however infre quently associated with heart disease and the protected life of its victims seems to guard them from early onset of the so-called degenerative types of heart disease Special shock therapy as by the use of Metrazol or electricity for this

or other psychoses rarely if ever hurts the normal heart except for the induction of temporary disturbances of rhythm in some cases slight unimportant changes in the electrocardiogram have also been noted

General paresis, a disease of the central nervous system due to syphilis is frequently complicated by syphilitic aortitis it has been estimated that about 20 per cent of these paretics are so affected

Senile dementia is often attended by coronary heart disease in keeping with the widespread arteriosclerosis that is present but the sheltered invalid existence renders the prognosis better and symptoms fewer than in the average individual with coronary heart disease On the other hand the mental state may render the diagnosis and treatment of angina pectoris myocardial infarction and early stages of congestive heart failure difficult or in some cases impossible as indicated by the significant finding of cardiac rupture in a majority of cases (16 out of 22) of myocardial infarction in the Massachusetts State Psychopathic Hospitals only 2 of the cases had been diagnosed as coronary occlusion during life (Jetter and White, 1944)

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CHAPTER 23

OTHER ETIOLOGIC FACTORS AND RELATIONSHIPS

Neoplasms Among the rare and relatively unimportant causes of heart disease are cardiovascular neoplasms It is doubtless because of their rarity and pathologic interest that they have been so often reported in the medical literature All kinds of tumors both primary and secondary including malignant lymphoma (Hodgkin s disease lymphoblastoma) have been found in the heart and pericardium Metastases from malignant disease elsewhere are much more numerous than primary malignancy Mahaim has written in recent years (1945) an authoritative book on the subject of cardiac tumors and polyps

Primary tumors of the heart have been reported to occur about once in 2 000 cases that come to necropsy (0 05 per cent) 75 per cent of such tumors are benign (Lymburner 1934) On the other hand metastatic malignancy of the heart and pericardium has been discovered in 118 out of 11,100 consecutive cases autopsied at the Cleveland City Hospital from 1919 to 1939 (1 1 per cent) these metastatic malignancies involving the heart and pericardium made up 10 9 per cent of the 1 082 cases of malignant disease in the whole series and were especially common with carcinomas of the bronchus and of the breast which were found in 48 per cent of the cardiac and pericardial cases (Scott and Garvin 1939) In another series metastatic lesions in the heart were discovered about once in 200 cases of malignant disease elsewhere in the body (0 6 per cent) (Lymburner 1934) Of primary tumors there have been reported in the order named most commonly myxoma sarcoma and rhabdomyoma less often carcinoma fibroma lipoma angioma cystoma papilloma teratoma and epicardial epithelioma In 1922 a review of the literature revealed the record of 150 cases of primary tumor of the heart 40 of which were sarcomas a new case of primary sarcoma was reported then (Goldstein) During the next 25 years over 50 more cases of primary cardiac tumor were reported including myxoma carcinoma sarcoma and xanthoma The new case of primary sarcoma of the heart reported by Wier and Jones in 1941 raised to 76 the total number of such tumors then on record More cases

were added in 1948 (Shelburne Halhuber and Kapferer) and a primary sar coma of the abdominal aorta has also been reported (Nencki 1946) In a reported series of 3 000 consecutive autopsies there were no primary heart tumors but there were 6 cases of secondary cardiac neoplasm originating twice in the uterus and once each in rectum kidney gallbladder and lung (Thorel 1903 1907) this illustrates not only the preponderance of secondary cardiac



FIG 117 Metastatic melanotic sarcoma showing many lesions throughout the myo cardium of both ventricles and septum of the heart (Kindness of Dr Pedro Castillo Havana Cuba)

tumors but also the multiplicity of the original tumor sites Among cardiac metastases malignant melanoma (Figure 117) has held a prominent place 4 cases having been added in 1939 (Moragues) to the 23 on record and at least 5 more have been reported since (Raven 1948 Lefkovitz 1948 Ritz 1949) A recent report of 30 cases of metastatic cardiac tumors has been pub lished by Piotti (1949) consisting of 23 carcinomas and 7 sarcomas in 17 men and 13 women the diagnosis was correctly made ante mortem in 20 of the cases Eight of the primary tumors were bronchial (6) or pulmonary (2) Tachycardia was the most common sign

Primary sarcoma of the pericardium has been reported in 11 cases 10 collected in 1931 (Yater) and one added later (Steuer and Higley 1935) Metastatic pericardial malignancy secondary to a lung tumor may be very

extensive (Figure 118) Bloody pericardial fluid is commonly found in malignant disease of the pericardium

Any heart chamber may be the site of neoplasm whether primary or secondary but the right chambers are more often involved than the left doubtless because the tumor is so often spread by the blood stream (Lymburner 1934) even the node of Tawara can develop its neoplasm (Mahaim 1942)

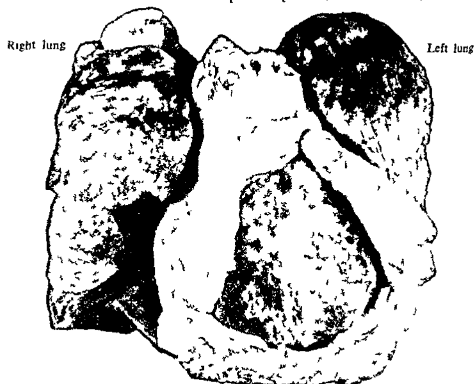


FIG 118 Photograph showing extensive malignancy (carcinoma) of the pericardium secondary to a tumor which is visible at the apex of the right lung The heart is somewhat compressed by the massive cancer surrounding it (Kindness of Drs Tracy Mallory and Benjamin Castleman Massachusetts General Hospital Boston)

Only rarely has it been possible to diagnose neoplasms in the heart before death in the past but that is changing now as noted in Piotti s report above As a rule they are relatively unimportant metastases or primary growths discovered incidentally at postmortem examination in persons dying of malignant or other disease elsewhere than in the heart In rare cases they may weaken the heart wall or produce heart block (atrioventricular or intraventricular) or other arrhythmias or embarrass the circulation otherwise by their size causing cyanosis and even simulating valvular disease by obstructing the valve ostia hence in heart trouble of unknown cause they should be thought of and looked for clinically Roentgen ray examination (showing unexpected heart size and shape) the discovery by electrocardiogram of atrioventricular or bundle branch block or T wave changes not otherwise explained the find

ing of a pericardial friction rub or effusion apparently not the result of infection and the presence of neoplasms elsewhere afford the most suggestive evidence The prognosis is serious except in the case of a few benign tumors and yet as a rule the individuals affected die of other than the cardiac involvement There is at present no adequate treatment for cardiac neoplasms surgery radiotherapy and chemotherapy of the tumor cells have not yet been sufficiently developed although life may be somewhat prolonged by radiotherapy in certain cases especially in those of malignant lymphoma

Poisoning other than by infections The effect of infectious toxins on the heart has already been discussed there remains the consideration of the effect of other poisons or possible poisons Fortunately any destructive myocardial effect of *heavy metals* as in arsenic bismuth and mercury poisoning is very rare and fatal results come as a rule not from the cardiac involvement but chiefly from the damage to other organs in particular to liver and kidneys Mercury now in very common use as a diuretic has been surprisingly well tolerated but in rare instances it has caused renal damage and in nearly unique cases collapse or sudden death of uncertain (perhaps cardiac) nature Phosphorus poisoning may depress the *T* waves and the *S T* segments (Dathe and Nathan 1946) There has been no observation of direct injury to the heart in lead poisoning *Illuminating gas* (carbon monoxide) has been reported to have caused necrosis in the myocardium and in the media of cerebral arteries of persons dying of its effect (Grunewald 1926) and electrocardiographic abnormalities such as a v block (Almgren 1946 Casolo 1947) Certain other poisons taken as food have been found to influence the heart for example the mushroom *Amanita phalloides* has been reported to have been the probable cause of temporary right bundle branch block (Hyman 1928) Central American snake venom has been noted to depress the *T* waves and *S T* segments and to prolong the *Q T* interval (Garcia Carrillo 1947) and the scorpion s bite can cause tachycardia and arrhythmias (Celoria and Sloer 1948)

Drug poisoning The drug most likely to poison the heart is *digitalis* itself which is used so often to control heart failure If given in excessive dosage digitalis may easily irritate the heart producing premature beats (extra systoles) atrioventricular block sinoatrial block or even atrial standstill atrial paroxysmal tachycardia atrial fibrillation ventricular paroxysmal tachycardia with or without alternation in direction of the ventricular complexes in the electrocardiogram and in rare instances ventricular fibrillation and death La Due (1942) has produced myocardial necrosis fibrosis and atrophy in 44 per cent of dogs which he subjected to daily intravenous doses of large amounts of digitalis It is very helpful to follow electrocardiographically the administration of saturating dosage of digitalis thus watching for some of the signs of poisoning as indicated by excessive inversion of the *T* waves and especially of the *S T* segments by prolongation of the P R interval (atrioventricular block) by the appearance of ventricular premature beats occurring bigeminally and if the poisoning is of dangerous degree by the onset of ven

tricular paroxysmal tachycardia Such electrocardiographic signs indicate that a considerable percentage of the lethal dose of the drug has already been ad ministered Other indications of digitalis poisoning should also be looked for namely anorexia nausea vomiting and visual disturbances (cloudy or colored vision) Diarrhea is a less common toxic effect of the drug The possibility of a deleterious toxic influence of digitalis on the heart is an important reason for not administering the drug carelessly Digitalis poisoning became more common in this country for a while on two occasions in recent years first after the strength of American preparations was raised some 30 to 50 per cent dur ing the period of the eleventh edition of the *U S Pharmacopeia* 1936 to 1942 (Bland and White 1941) dropping since the publication of the twelfth edition in 1942 to a 16 to 30 per cent increase over the strength of the standard unit prior to 1937 and second when digitoxin began to be used more freely with large daily rations of 0 2 mg or more (see Chapter 30) Fortunately seri ous poisoning of the heart by digitalis given by mouth is unlikely to happen because of the emetic effect of large doses

Quinidine sulphate another very helpful drug that may poison the heart, has been used considerably in recent years in the treatment of cardiac arrhyth mia particularly atrial fibrillation This medicine may have a harmful effect on the heart as well as the beneficial effect of abolishing atrial flutter and atrial fibrillation Such harmful effect is shown by the presence of sinoatrial depression intra atrial block and intraventricular block and rarely premature contractions paroxysmal tachycardia (atrial or ventricular) and even ven tricular fibrillation or standstill It is probable that the rare cases dying sud denly during quinidine therapy have for the most part suffered direct fatal quinidine effects on the heart in particular total standstill due to paralysis of both sinoatrial and atrioventricular nodes The drug should be employed only with great care if large doses are administered and then only under close observation with electrocardiographic control Quinidine therapy will be dis cussed further in Chapter 33

Other drugs are less frequently the cause of heart trouble although occa sionally when one of them is given too vigorously such as *arsenic* in large dosage in the treatment of syphilis heart failure may be precipitated The *salicylates* including aspirin may cause serious poisoning and even death in rare cases which show postmortem petechial and larger hemorrhages scattered throughout the body and focal necroses (Krasnoff and Bernstein 1947)

The intravenous therapeutic use of *calcium* in high concentration can pro long systole, depress the cardiac pacemakers and conduction tissue (to cause bradycardia and heart block), and increase the excitability of the ventricular muscle (to produce ectopic beats) (Clark 1941) *Potassium* in large dosage elevates the *T* waves of the electrocardiogram and widens the *QRS* waves while tending to produce abnormal peripheral sensory reactions (paresthesia) it should be employed cautiously in renal disease since the poisonous concen tration of potassium in the blood is a common occurrency in renal insufficiency (Thomson 1939 Keith et al 1942)

Tarail (1948) noted that electrocardiographic changes begin to appear when the concentration of serum potassium lies between 6 8 and 7 6 milliequivalents per liter and are consistently found at amounts greater than 7 8 m Eq /L A fatal concentration in man is over 10 0 m Eq /L when diastolic standstill occurs with generalized flaccid paralysis (Finch et al 1946) Sodium and calcium salts blood and glucose may correct the effects when not extreme Low potassium blood levels can also affect the electrocardiogram flattening the *T* waves and prolonging systole

Metrazol used to cause convulsions in psychopathic states may induce extrasystoles of little import *Ergotamine* raises and *adrenaline* lowers the *T* waves through their vagal and sympathetic effects respectively (Hartwell et al 1942) and *morphine* has long been known to produce vagal effects on the heart with slowing of the rate delay in conduction lowering of the *R* waves and raising of the *T* waves (Einthoven and Wieringa 1912) *atropine* neutralizes this effect and when given alone lowers the *T* waves (Hartwell et al 1942) Various other drugs may produce electrocardiographic changes for example *emetine* (for amebiasis) which lowers the *T* waves and delays conduction and *antimony* (Fuadin and tartar emetic for schistosomiasis) which lowers the *T* waves and prolongs systole The *sulfonamides* may cause myocardial necrosis in rare cases but penicillin does not do so

Finally *chloroform* as an anesthetic has long been known to have a poison ous effect on the heart causing extrasystoles and even ventricular fibrillation in animals and probably by this same mechanism causing sudden death in rare instances in man chloroform and the newer related anesthetic cyclopro pane are therefore far more dangerous anesthetics than ether and most other preparations especially if the heart is already diseased and irritable

There are a few substances used widely by mankind for pleasure or stimu lation or because of habit that have as a rule but little deleterious effect on the heart the literature is full of conflicting statements about their harmless or pernicious influence Such substances are alcohol tobacco tea and coffee

Alcohol in strong concentration and large amounts can perhaps injure the myocardium but certainly to a far less extent than more sensitive organs like the liver and brain In small or moderate amounts it has no harmful effect at all but rather a vasodilating action which relieves or prevents angina pectoris Small quantities of alcoholic beverages through their relaxing effect may benefit individuals who are depressed or under nervous tension and it is even possible that regular daily use of light wine or beer in moderation may favor the maintenance of good health In fact it has been noted by several observers (Cabot 1904 Leary 1931) that arteriosclerosis is rare in cases of excessive alcoholism suggesting a protective influence in that respect though less than nothing is gained if liver brain and morale are seriously damaged in the process The cardiovascular reaction following acute alcoholism is moreover often unfavorable producing neurocirculatory asthenia paroxysmal arrhyth mias increase in angina pectoris or precipitation of congestive failure in

cardiac patients Finally a considerable use of alcoholic beverages does not protect a person from serious coronary heart disease even in the forties as I have found in the case of several patients

Tobacco varies greatly in its effect according to the individual and also according to the tolerance produced by habit It causes no actual heart disease but it may in large amounts or in susceptible persons excite sinoatrial tachycardia premature contractions or paroxysmal tachycardia, and in extreme cases paroxysmal atrial fibrillation Palpitation may be caused by these arrhythmias In the majority of individuals particularly hypertensive patients the blood pressure (both systolic and diastolic) is raised appreciably and even the metabolic rate In a few individuals with coronary heart disease the use of tobacco has been known to precipitate or to aggravate angina pectoris and to cause tachycardia temporary changes in the *T* waves of the electrocardiogram, and a harmful effect on the coronary circulation In fact in one healthy young man the inhalation of tobacco smoke has been observed temporarily to cause dizziness and inversion of the *T* waves in Leads 1 and 2 of the electrocardiogram so that they resembled for a few beats the *T* waves of coronary heart disease (Graybiel Starr and White 1938), whether this change is to be attributed to excessive sympathetic nerve stimulation to coronary arterial constriction or to a direct toxic myocardial effect we do not know but we are inclined to accept the first of these explanations Various recent investigations (Roth et al 1944, Boyle et al 1947 Levy et al, 1948 Mathers et al 1949) have compared the effects of inhaling tobacco smoke with the injection of nicotine and have found them to be similar with increase of heart rate and blood pressure and lowering of the *T* waves of the electrocardiogram tachycardia is the simplest gauge of hypersensitiveness to tobacco (nicotine) Thus there is after all such a condition as a tobacco heart but it is a state of functional derangement of the heart and circulation and not organic heart disease When the so called denicotinized tobacco which contains only ⅓ to ⅟ or less of the amount of nicotine found in ordinary tobacco is used the heart is much less likely to be disturbed in individuals who are sensitive to the plant Tobacco also causes a peripheral vasoconstriction with lowering of the skin temperature (Weatherby 1942) and has been suggested as a factor in causing thromboangiitis obliterans a disease of youth and middle age of unknown etiology to be discussed in Chapter 28 The chief disadvantage of tobacco in my experience has been the induction of cardiospasm and even gastritis as disagreeable complications in my cardiac patients or as trouble simulating the angina pectoris of coronary heart disease Because of the fact that tobacco (nicotine) is, in most persons a pressor agent it is wise to avoid its use in the presence of hypertension Incidentally it is of interest that alcoholic beverages do not neutralize the vasoconstricting effect of tobacco (Roth and Sheard 1947)

Tea and *coffee* do not cause heart disease but by nervous stimulation they are frequently the cause of increased heart rate and palpitation and in some

susceptible individuals of premature beats or paroxysmal tachycardia on the other hand they may be helpful in cases of mild Cheyne Stokes respiration

A few years ago much excitement was engendered by the discovery of some *lithium* poisoning secondary to too liberal use of lithium chloride as a substitute for sodium chloride in low sodium diets for congestive heart failure in particular Few serious cases were found among many thousands but unfortunately this excellent taste substitute was largely abandoned whereas under proper control and in small dosage (e g a few drops of a 25 per cent watery solution amounting to not more than 0 05 gm a day) it is quite harmless and helpful The symptoms of lithium poisoning are not cardiac but include in particular weakness of muscles and mental confusion

Finally *poisons may be generated in the body* itself to irritate or damage the heart The most frequent well marked example of this is in the case of uremia where abnormal heart action and distorted electrocardiograms have sometimes been found doubtless the result of the toxic effect of the high content of potassium in the blood Irritation of the heart as shown by the appearance of premature beats may sometimes be only a reflex nervous manifestation which doubtless explains in large part the relationship of such conditions as indigestion as well as of most focal infections to cardiovascular symptoms A slow pulse due to sinoatrial bradycardia apparently a vagal effect is occasionally prominent in cases of catarrhal jaundice the toxic effect of severe hepatic insufficiency is manifested especially by stupor and depressed respiration

Disorders of nutrition Avitaminosis Obesity Fatty infiltration and fatty degeneration Gout Much has been said about malnutrition and the harmful effects of avitaminoses and much of it is true but overemphasis on these conditions has had two harmful results (1) the excessive use of all kinds of expensive vitamin preparations and (2) the relative neglect of overnutrition which with or without obesity is doubtless more injurious to more persons than is undernutrition It may well be that especially in the U S A today overnutrition with its common companions diabetes coronary atherosclerosis and hypertension is on the way to becoming a major threat to the health of the people An important consideration about malnutrition especially the avitaminoses is that the deficiency is only rare in one food element whether protein vitamin B_1 vitamin C or vitamin D or other factor the deficiency is almost invariably multiple

Beriberi a disease which is primarily the consequence of vitamin B_1 deficiency (tropical avitaminosis) has been shown to cause hydropic degeneration (intracellular edema) of the myocardium particularly of the right ventricle with cardiac dilatation and failure in rare cases Electrocardiograms have shown in such cases small complexes negative *T* waves in Lead 1 and slight aberration of the ventricular complexes Beriberi was once a common disease in the Orient but it has been much reduced in the last generation by

change of diet from that of polished rice low in the essential vitamins in the Occident beriberi has never been common but it is occasionally seen in severe alcoholism in markedly restricted intake of food as in Negro infants and young children reported by Waring (1929 1938), and in a few individuals with severe gastrointestinal disorders or psychiatric conditions resulting in semistarvation with avitaminosis Heart disease with enlargement and peripheral vasodilatation with rapid blood flow are found complicating only the more severe cases of beriberi often attended by a polyneuritis Beriberi is one of the few conditions (another is arteriovenous fistula) which may result in congestive heart failure even though there continues to be an increased cardiac output (Weiss and Wilkins 1937, Burwell and Dexter, 1947) As a complicating factor in other conditions especially in heart failure itself with poor appetite and malnutrition avitaminosis of mild to moderate degree may cause additional trouble and require specific therapy The edema of wet beriberi is largely the result of congestive heart failure but may also be favored by malnutrition with low serum protein Relief is obtained primarily neither by digitalis nor by diuretics but by the administration of antineuritic vitamin B_1 intravenously in severe cases but by mouth with success in most patients

Scorbutus (scurvy), due to lack of vitamin C carries with it a tendency to hemorrhage which may involve the heart and pericardium as well as other parts of the body the heart muscle is said to show degeneration in scurvy

Rachitis (rickets) due to lack of vitamin D when very severe is also associated with abnormality of the heart consisting chiefly of dilatation and failure in a series of eleven children dying suddenly with rachitis each child showed at postmortem examination left ventricular dilatation (Meixner 1928)

Pellagra although an important and common deficiency disease has not been found to be associated with any specific cardiac pathologic abnormalities except for changes in the *T* waves of the electrocardiogram (Rachmilewitz and Braun 1944) circulatory troubles found in such cases are to be ascribed for the most part to lack of vitamin B_1 or to the hypoproteinemia of starvation or to a coincident heart disease Nicotinic acid is the specific treatment for pellagra but all of the vitamin B group should also be given to cover the combined deficiencies present

Starvation may cause generalized edema in victims of famine such edema may be the result of depression of renal excretion of sodium (Berkman 1950) or caused by disturbed osmotic pressure due to low blood protein (albumin) as in cases of nephrosis' and is not a manifestation of cardiac failure The critical level of protein in the blood serum below which nutritional edema appears is about 5 gm per 100 cc the albumin globulin ratio is often reversed Adequate diet especially rich in protein and vitamin B_1 because of a frequently associated avitaminosis quickly clears up this edema Starvation decreases the heart size cardiac rate and output blood pressure and electrocardiographic voltage while increasing the duration of systole (Ellis 1946 Simonson et al 1948), it has been estimated that for a loss of 30 per cent in body weight there is a loss of 20 per cent in the heart weight (Keys 1948)

Obesity may or may not be attended by heart disease It is common for obese individuals because of lack of physical training and fitness and because of their excessive weight to develop the effort syndrome easily but this does not signify heart disease It is however now well known that obese persons have more hypertension and atherosclerosis and live shorter lives than do per sons who are lean or of average weight and yet overnutrition continues to be the rule in this country Most persons add 20 pounds or more of weight after the age of 25 years and such increased weight is due to the deposition of fat not just under the skin but in the liver as well and in the coronary artery walls it would seem to be common sense to avoid adding fat when there is already good nutrition

There is a greater tendency also for obese individuals than for thin persons to store fat in and about the heart especially in the interventricular and atrio-ventricular grooves and over the surface of the right ventricle into the musculature of which it may actually slowly penetrate splitting the wall and favoring atrophy of the myocardium and even rupture or failure of the right ventricle Fat may be deposited subendocardially especially in the course of the atrio-ventricular conduction system in an amount said to be sufficient to cause pressure and atrophy and under special strain even sudden death Of these last mentioned effects of fat in and on the heart we have however no proof

Two common important sources of error in the estimation of heart size by roentgen ray arise as the result of obesity and fat deposits In a stout person especially when there is much abdominal fat the diaphragm tends to be high in position and the heart placed horizontally Such a horizontal heart shadow shows an increase above the average normal both in transverse diameter and in area (see Chapter 7) Hence a correction must be made in such cases in the estimation of heart size When because of the horizontal heart position the transverse diameter approaches the long diameter in measurement (usually it averages 1 5 cm less) 1 to 2 cm may be subtracted from the transverse diameter and about 25 sq cm from the area in calculating the heart size Also in such cases the aorta tends to be kinked by the upward pressure and looks much wider in the anteroposterior view than it actually is sometimes resulting in an erroneous diagnosis of aortic dilatation. Views during deep inspiration and also with the subject in the oblique positions help to prevent errors of roentgen ray interpretation in obese individuals

The other source of error in roentgen ray interpretation arises from the presence of a triangle of fat usually some 2 to 3 cm wide at the pericardial diaphragmatic angle on the left just beyond the cardiac apex (Figure 7 shown on page 39) this is more common in but not limited to obese persons An extrapericardial layer of fat at the right heart border may also cast an appreciable and sometimes confusing shadow Unless care is taken the transverse heart diameter and the area may be erroneously measured and misinterpreted (McGinn and White 1936)

That there is an actual *fatty heart (cor adiposum)* consisting of *fatty infil tration* as described above has been proved by pathologic studies but the

clinical significance of the condition is not clear, the truth probably rests between the two extreme views that the fatty heart is a common and dangerous condition and that it does not exist at all Still more doubtful is the association of the cor adiposum with general obesity, they often are associated but there are also frequent exceptions the fatty heart being found in the absence of obesity and obesity being found without the fatty heart More study is needed to solve this problem

Fatty degeneration of the heart may ensue in cases of marked fatty infiltration but it is strictly a different condition and results as a rule more or less acutely from the toxic influence of infectious or noninfectious poisons and from the cutting off of the blood supply to the myocardium by severe anemia (see below) or by the narrowing or occlusion of the coronary arteries It is therefore not primarily related to obesity

Gout is often associated with excessive atherosclerosis and coronary heart disease which in the younger age group is frequently attended by an abnormally high content of uric acid in the blood but there strictly is no such entity as a gouty heart

Blood diseases Serious cardiac dilatation may occur with high grade *anemia* and may cause functional insufficiency of the mitral and of the tricuspid valves and in rare cases also of the aortic valve In severe anemia of any type the circulatory rate is increased with elevation of pulse pressure stroke volume minute volume cardiac rate and output and oxygen consumption and with decrease in the arm to tongue circulation time When the hemoglobin content drops below 25 per cent (3 5 gm) the cardiac dilatation may become extreme and congestive heart failure may appear without pre-existing heart disease in one series of 10 patients with very severe anemia (Tung et al 1937) 6 showed marked congestive failure with no other discoverable cause than the anemia Treatment for and recovery from the anemia usually results in a disappearance of the congestive failure and a return of the heart size toward or to normal Anemia is one of the four important clinical conditions in which congestive heart failure is attended by an increased cardiac output the other three being beriberi thyrotoxicosis and an arteriovenous fistula

Electrocardiographic abnormalities are also common in severe anemia in one group of 76 anemic patients 23 showed abnormal records (Szekely 1940) and in another of 45 cases 10 had such electrocardiograms (Ellis and Faulkner 1939) The abnormalities consist of flattening or inversion of the *T* waves depression of the *S T* segments and a tendency to low voltage of the *QRS* waves With correction of the anemia the electrocardiogram usually returns to normal

It may be concluded that the heart trouble in anemia is due to the combination of the myocardial anoxia and the increased work of the heart

In *hyperchromic* commonly *pernicious anemia* years ago before the institution of specific liver therapy the heart was commonly found at postmortem examination hypertrophied and dilated with fatty degeneration of the myocardium in streaks farthest from the fresh blood supply that is at the venous

ends of the capillaries giving rise to a curious gross appearance which was called the tiger or 'tiger lily heart Although it was the anemia and not the heart trouble that was usually responsible for death congestive failure and angina pectoris were seen in rare cases Now that specific remedies have been introduced for pernicious anemia protection of the heart has been possible against the changes noted above In rare cases however angina pectoris has apparently been precipitated during specific treatment of pernicious anemia probably through the accompanying increase in blood volume

Hypochromic (secondary) anemia if slight has no deleterious effect on the heart but if it is severe there may result the same fatty changes dilatation and hypertrophy that were at one time common in primary pernicious anemia Also angina pectoris may occur in rare cases even in the absence of coronary disease (Elliot 1934) Systolic murmurs at apex and base are common in severe anemia of any type due to left ventricular dilatation with mitral regurgitation and to dilatation of the aorta and pulmonary artery Even diastolic murmurs mitral and aortic and possibly even pulmonary are not rare in severe cases the pathogenesis of such murmurs is undoubtedly concerned with the dilatation of the heart With a much dilated left ventricular cavity and a rapid blood flow such as is usually found in marked anemia a mitral diastolic murmur is produced by a relative mitral stenosis though the mitral valve itself is normal or even slightly dilated while weakness of the aortic and pulmonary valve rings may result in their stretching with resulting regurgitation Such murmurs tend to come and go according to the functional state of the heart Gunewardene (1935) has called attention to the frequent wrong interpretation labeled mitral stenosis of cardiac dilatation in severe anemia in India

In *sickle cell anemia* not only may the heart resemble the rheumatic heart with its enlargement and various murmurs but the course of the exacerbations of the disease over a period of years may resemble rheumatic fever the pains however involve the long bones rather than the joints and are not relieved by salicylates (Klinefelter 1942)

With the reverse condition *polycythemia* (or erythremia) the increased bulk of blood is an added burden for the circulation but strain on the heart is largely prevented by peripheral vasodilatation The capillaries are uniformly found dilated in cases of polycythemia whether primary (Vaquez-Osler disease) or secondary to congenital heart disease or chronic pulmonary disease Vascular lesions thromboses especially are occasional accompaniments of polycythemia a study of 98 cases of polycythemia vera and of 35 cases of relative polycythemia by Norman and Allen (1937) revealed in about a third of the cases a variety of vascular complications—erythromelalgia coronary thrombosis with myocardial infarction angina pectoris occlusive disease of the peripheral arteries cerebral hemorrhage or thrombosis intra abdominal vascular thrombosis phlebitis and vasomotor neuroses

Oxyhemoglobin may be limited in the blood by the existence of methemoglobinemia acquired as in the case of carbon monoxide or acetanilid poison

ing or congenital as in the case of 5 members of one family reported by Gibson and Harrison (1947) it is important to distinguish the cyanosis in such cases from that of cardiac or pulmonary disease and from the reduced silver in the skin in argyria

In *lymphatic leukemia* and less often in *myelogenous leukemia* the myocardium as well as many other organs and tissues of the body may be found infiltrated with the abnormal leukocytes but this finding is merely a minor part of these fatal diseases Hodgkin s disease (malignant lymphoma or splenic anemia) is discussed earlier in this chapter under the heading Neoplasms it may be attended by severe anemia

Trauma Injuries of all varieties may involve the cardiovascular apparatus in any part—heart pericardium great vessels arteries or veins Injuries of blood vessels are very frequent and even trauma of the heart itself is not at all rare There may be penetrating wounds of the heart by gunshot bomb or shell fragments, knife dagger sword bayonet or other instrument such as were seen by the thousands during both World Wars Injury may come in directly by contusion from blows or falls by crushing or by intense jarring Finally there may be spontaneous rupture of valve cusp chordae tendineae papillary muscle atrial or ventricular wall or aorta When rupture of any sort comes by indirect violence or spontaneously heart disease is usually found to underlie the injury—for example bacterial endocarditis in the case of rupture of valve cusp or chordae tendineae cardiac infarct in the case of rupture of heart wall septum or papillary muscle (see Chapters 21 and 25) and aneurysm or medial necrosis in the case of ruptured aorta (see Chapter 28) Sometimes however even when the trauma does not seem great clean cut rupture (usually linear tears) of heart wall or aorta may occur without any evidence of local disease at postmortem examination such cases are to be explained by an unusual amount of strain exerted at the moment of full distention of heart chamber aorta or valve cusp the tissue in question being perhaps congenitally weak A defect in the media of unexplained etiology (Erdheim 1929—see Chapter 28) no doubt accounts for some aortic ruptures The reports of proven cases show that serious or fatal injury can come even to a normal heart or aorta from indirect or direct trauma as in striking the surface of the water in diving without any penetrating wound The greater the injury the more likely of course is heart damage See Figure 119 for rupture of papillary muscle

Contusion or even partial rupture of the heart wall may also occur and because of the usual recovery of such cases may pass notice (Schlomka and Schmitz 1932 Bright and Beck 1935) A steering wheel injury produced by sudden compression of the anterior chest wall of the operator of a motor car by his steering wheel at the time of an accident is doubtless a cause of contusion of the heart (Bright and Beck 1935) but just how common it is we do not know there is considerable danger now of its exaggeration In these days of claims for compensation for injuries by everything under the sun the steering wheel cardiac contusion is having its share of publicity and has

already become the cause of at least some cardiac or traumatic neuroses As a matter of fact the heart is a very mobile organ in the chest and is likely to escape injury whether the trauma is penetrating or not, in reviewing cases of wounds of the heart Elkin (1938) noted that in his experience only 2 per cent of penetrating wounds of the chest injured the heart Contusion or even rupture of the heart has been recognized as an occasional result of blast in juries resulting from bomb explosions in World War II or even as an industrial



FIG 119 Photograph of traumatic injury to the heart Anterior papillary muscle of the left ventricle torn from its base (as shown by the arrow) in case of a young man run over by a truck

hazard (Miller 1947) The only clue to heart muscle contusion in some cases is electrocardiographic evidence of fresh myocardial damage an electrocardiogram should be obtained whenever possible shortly after any severe thoracic injury Temporary changes especially in the *T* waves may follow a penetrating or contused lesion of the heart muscle and like the electrocardiogram in acute myocardial infarction aid in the localization of the damaged area

In the last edition of this book (1944) I wrote that coronary thrombosis with myocardial infarction is not the result of trauma so far as we know at present from the experience of many observers of many hundreds of cases except in a few instances of advanced coronary atherosclerosis and narrowing to start with and in others where because of an incised wound of the heart wall it has been necessary to ligate a major coronary artery in the course of

surgical repair Since then however a case has been reported of a boy of ten years who succumbed to acute coronary thrombosis involving the left descending artery a few minutes after three rounds of a boxing match necropsy showed only slight atheromatous changes in the intima (Jokl and Greenstein 1944)

In rare cases recovery may take place after rupture or penetrating wound of the heart especially in the case of the latter injury, if operative relief can be quickly afforded Many cases of successful healing of sutured wounds of the heart have been reported There may be no sequelae after such wounds and the heart, years afterward may be found to be carrying on its function in a normal manner on the other hand serious after-effects may appear A striking case in a youth has been reported of perforation of the anterior mitral valve cusp (gunshot wound) producing pure mitral regurgitation and followed by enormous enlargement of the heart with hypertrophy and dilatation of all *four chambers and death after several years from congestive failure* (Adam 1927) In this last mentioned case there was also an adherent pericardium following the hemopericardium produced by the injury but this had little or nothing to do with the cardiac enlargement and failure Such a coincidental pericardial lesion may complicate any case of cardiac trauma Another interesting instance is also on record of death from heart failure in the case of a young man 14 months after rupture, by a crushing injury of the cusps of his *normal aortic valve* (Kissane et al 1936) *Heart block has been noted after* cardiac trauma (Coffen et al 1941)

Successful suture of wounds of the aorta also has been proved possible as in a case reported by Blalock (1934) and of vena cava too (Barnes 1938)

One of the chief hazards of penetrating wounds of the heart is that of *cardiac tamponade from hemopericardium* This may come quickly in the course of a few minutes or an hour or so and to the inexperienced eye may simulate shock The pulse becomes small and rapid with very low pulse pressure and paradoxical character the neck veins become engorged (unless there is a coincident vascular collapse) because of their inability to empty into the acutely constricted or compressed heart and death may ensue shortly unless surgical relief is afforded The heart wall must of course be sutured to prevent further bleeding, but the emergency measure is paracentesis (or better incision) of the distended pericardium as in a case reported by Rajasingham (1939)

Furthermore *foreign bodies* may enter the heart wall or chambers and remain there for years perhaps with little or no harmful effect Extraordinary instances have been reported of projectiles migrating to the heart by way of the great veins from distant wounds in thigh abdomen or neck and in two cases (Boeckel 1917 and LaRoque 1926) of projectiles migrating from left ventricle and aorta respectively as emboli to block the femoral artery with resulting gangrene of the leg in Boeckel s case Another very interesting case has recently been reported by Shapiro (1941) of migration of a hollow needle used for intravenous injection from arm vein into the heart and through the

heart wall to lie eventually in the prepericardial fat between heart and diaphragm

Trauma to the myocardium may result from excessive exposure to the roentgen ray This has been shown in experimental animals and found at autopsy in a few patients treated by radiotherapy for intrathoracic tumors Clinical evidence of such injury has not yet however been demonstrated convincingly

Arrhythmias are sometimes induced by trauma but as a rule they are unimportant temporary and either subside spontaneously in the course of a few days or weeks or are easily controlled by treatment (see Chapters 32 and 33) this is true even of absolute arrhythmia (atrial fibrillation) which is likely to occasion unnecessary alarm except in rare persons in whom congestive heart failure may be induced by the extra strain of the atrial fibrillation when there is already present chronic heart disease with limited reserve

Electric shock whether accidental (Koeppen 1940) or induced in the therapy of psychoses (Streit 1941 Hejtmancik Bankhead and Hermann 1949) can produce all kinds of disorders of the heart rhythm but especially extrasystoles changes in the *S T* segments and *T* waves have been reported lowering of the former and at first elevation and later depression of the latter Electrocution results in death from (or with) ventricular fibrillation (following quickly after the appearance of extrasystoles and bundle branch block) (Kountz personal communication 1943)

Finally the question of the relationship of *occupational hazards* to cardiac trauma is important and often very difficult Occasionally injuries received during work may traumatize seriously a perfectly normal heart but as a rule heart symptoms or signs that follow industrial strain or accidents are either merely those of neurocirculatory asthenia or neurosis in sensitive individuals or are due to the precipitation or aggravation of trouble in a heart already damaged or diseased The decision as to the relative responsibilities of accident or strain and of previous heart disease in the production of symptoms and signs is often a great problem sufficient to tax the wisdom of the most experienced physician or judge A most interesting problem of sudden cardiac death on Monday mornings of employees of powder plants when hurrying back to work after being out of the nitrite atmosphere for some 60 hours during the weekend was a case in point (Drinker personal communication 1935) this hazard was eliminated when the plants were adequately ventilated Even after an adequate appraisal of the relative responsibilities of trauma or other strain and of pre-existing heart disease in the production of cardiovascular symptoms or signs of disability it is not always possible to adjust accident or industrial insurance compensation in accord because of faulty local laws or regulations that is in some places the decision must be all or nothing instead of a proper percentage of the total This faulty situation demands correction Of the greatest importance in this connection is the value of careful routine (annual) cardiovascular examination of all industrial employees

Thoracic and spinal deformities An appreciable and sometimes serious handicap to the action of the heart and circulation may be occasioned by deformities of the thorax or spine particularly marked *kyphoscoliosis* The strain, however, may be more pulmonary than cardiac with much diminished vital capacity of the lungs but almost always both systems respiratory and circulatory, are involved with resultant pulmonocardiac failure (Chapman Dill and Graybiel, 1939) The heart may be displaced (to the left with right scoliosis and to the right with left scoliosis) and deformed and the great vessels compressed so that left ventricle or right ventricle or both may have increased work to do with resulting hypertrophy and dilatation Or the re striction of thoracic movement in respiration may result in special strain on the right ventricle such as occurs in the case of the cor pulmonale In badly deformed individuals survival to old age is frequently prevented by the cardio-vascular strain as well as by pulmonary complications

Marked *depression of the sternum* (producing funnel chest or pectus ex cavatum) *may in rare cases seriously embarrass the heart* by flattening it anteroposteriorly and compressing the right atrium and right ventricle during expiration or by torsion of the great vessels usually however the heart is simply displaced to the left without any particular handicap unless the de formity is extreme with little mediastinal space between sternum and spine Operative relief is difficult but may be successfully carried out as in the series of cases operated upon by Sauerbruch (Sauerbruch 1931 O Shaughnessy 1940) and as has been done since 1943 by Sweet at the Massachusetts Gen eral Hospital

The presence of *cervical ribs* may occasion not only trophic disorders and disturbances of the peripheral circulation in the hands somewhat resembling Raynaud s disease and in some cases thrombotic and embolic obliteration of arteries of the arms and hands (Telford and Stopford 1931, Eden 1939) and even subclavian arterial thrombosis and hemiplegia due to cerebral embolism (Hoobler 1942) but it has also been thought responsible in some cases for disturbances of cardiac rhythm (premature beats atrial paroxysmal tachy cardia atrial flutter) due to irritation of cervical nerves

The *scalenus anticus syndrome* consisting of localized and radiating pain in and from the upper precordial and clavicular and shoulder regions and *trophic disturbances in either arm may simulate on occasion angina pectoris* but it is usually readily differentiated by the longer duration of the pain and variation with a change in shoulder and arm position It is caused by pressure of the anterior scalenus muscle or fibrous band representing rudimentary rib or middle scalenus muscle upon the subclavian artery (*with reduction of pulse* size and blood pressure) and lower portion of the brachial plexus it can be relieved by surgery with section of the offending structures (Rogers 1941 Adson 1947) or by skeletal traction in selected cases (DePalma 1948)

High altitude Aviation hazards Climate and weather *High altitude* in creases the work of the heart in attempting to supply to the tissues an adequate amount of oxygen the pressure of which in the inspired air is decreased be

cause of the decrease of atmosphere at points much elevated above sea level The influence of high altitude depends on several factors first the height above sea level second the individual s capacity to compensate for the oxygen decrease third the length of time the subject has lived at the high altitude and fourth the degree of physical activity at this altitude Below a height of 5 000 feet (about 1 700 meters) altitude has little or no effect between 5 000 and 10 000 feet it probably has a slight to moderate effect between 10 000 and 15 000 feet it has considerable effect and over 15 000 feet (5 000 meters) it has a very marked effect on the circulation Individuals vary greatly in their ability to adjust themselves physiologically to high altitudes and therefore in their ability to withstand *mountain sickness* which is due to low arterial oxygen saturation the cause of the difference is not clear, but it seems to depend in part at least on the capacity of the lungs to allow a rapid diffusion of oxygen from alveolar air to blood stream Tests of this capacity of an individual to endure the low oxygen pressure of high altitudes either on land or in the air may be made at sea level without the expenditure of time and money necessary for traveling to very high altitudes At an altitude of 15 000 feet the heart works about 20 per cent harder to accomplish 20 per cent less work than at sea level (Barcroft and associates 1922) An altitude of 10 000 feet is the more or less critical height above which mountain sickness is likely to occur The more prominent symptoms of mountain sickness are headache vertigo nausea dyspnea palpitation and weakness The electrocardiogram of normal soldiers at 15 000 feet has shown elevation of *S T* segments and inversion of *T* waves in several precordial leads corrected by descent to sea level (Alzamora and Monge 1949)

Aviation medicine which has developed of late by leaps and bounds under the stimulation of modern warfare includes not only the effect of high altitude as in mountain sickness which can be successfully combated by the inhalation of oxygen but also two other important circulatory strains namely (1) that of the centrifugal force on the blood mass resulting from intense acceleration of the speed of modern planes and from abrupt change in direction as in dive bombing in part at least controlled by special equipment which compresses the lower part of the body and by prone body position and (2) that of air embolism resulting from very rapid climbs to very high altitudes requiring control by preoxygenation and denitrogenation or by the maintenance of a more or less uniform atmospheric pressure protecting the aviator Very few cardiac deaths however have been recorded among several million passengers in air travel where the hazards are relatively slight (Graybiel 1941) Of the greatest importance in the selection of pilots and other air crew is testing them for their ability to stand these various strains since individuals vary greatly and in maintaining them in a state of physical fitness

Individuals who have lived long at high altitudes for example 15 000 feet or more acquire an ability not found in the newcomer to adjust the circulation to the low oxygen pressure The adjustment expresses itself by the development of polycythemia barrel shaped thorax and ability to undertake

relatively strenuous exertion which is impossible for the new arrivals That the adjustment is not adequate is shown by the uniform occurrence of cyanosis clubbing of the fingers and pulmonary emphysema in the case of natives of very high altitudes (Talbott and Dill 1936) the lowest oxygen saturation of arterial blood in a series of six healthy workmen resident at 17 500 feet studied by Talbott and Dill (1936) was 67 6 per cent (normal 95 per cent) while the average in the six was 75 per cent and in ten temporary residents 76 2 Removal to low altitudes or the administration of oxygen is necessary to combat the excessive anoxemia that comes with an acute pulmonary disease like pneumonia The degree of physical activity possible at high altitudes depends on the three factors already discussed even a native with good compensation is unable to perform at high altitudes an amount of work easily possible at low altitudes without symptoms of circulatory distress (chiefly dyspnea and tachycardia) Heart failure is rare at high altitudes unless there is already serious heart disease An increase in heart size especially right ventricular in natives living at 4 540 meters has been reported by Rotta (1947)

In contrast to the effect of low oxygen tension in the inspired air high oxygen atmospheres (up to 50 per cent of oxygen) have shown no deleterious effects in the case of 2 normal men and 28 patients with cardiac insufficiency who were kept in such atmospheres for periods of time ranging from 5 days to 7 months the patients were almost invariably benefited by such therapy (Richards and Barach 1934) Pure oxygen at atmospheric pressure inhaled for many hours may produce pulmonary edema in animals but has been well tolerated and very helpful in human patients (A L Barach personal communication 1942) there has been no proof of depression of the respiratory center in the brain by prolonged inhalation of high percentage of oxygen except in rare deeply cyanosed cases with extensive pulmonary disease who require the aid of a respirator adequately to take in oxygen and to blow off carbon dioxide

Very high atmospheric pressures may have harmful effects as in caisson disease with its hazard of the bends due to gaseous emboli of nitrogen in blood and tissues (Behnke 1940 Shilling 1941)

Extreme variations in *weather* have an important effect in cardiac patients *in precipitating or increasing disorders of function such as congestive failure* coronary insufficiency (angina pectoris) and arrhythmias Intense cold high winds and excessive humidity are especially harmful but as yet little adequate study has been made on this important problem In one series of cases attacks of coronary occlusion were found to be more frequent in winter than in summer (Bean and Mills 1938) but in another series in New England (White and Brasil 1935) the attacks were scattered quite uniformly throughout the months over a ten year period Effort angina pectoria is certainly more common in cold weather but it is important incidentally to note that in intensely hot weather physical effort which might precipitate cardiac symptoms is normally reduced to a minimum

Work and exercise Athletics Physical work and exercise do not primarily cause heart disease or heart damage except in the rarest cases (see below) though they may precipitate or aggravate symptoms and signs of heart disease already present and may temporarily exhaust the cardiovascular reserve even in a healthy individual There has been much written about the industrial heart the athletic heart and the military heart but final conclusions cannot yet be drawn from the insufficient data that we possess Suffice it to say that all three of these so called heart conditions are nothing more nor less in most cases than fatigue or effort syndrome especially marked in nervous individuals in whom it may amount to neurocirculatory asthenia in some cases there may be also hypoglycemia and in others who perspire much lack of sodium chloride relieved by glucose and by common salt respectively

Two other factors however are significant One is real trauma due to exercise or work that may cause either directly or indirectly rupture of some part of the heart or great vessels even when the heart is normal The other is the possibility in fact perhaps the likelihood of actual increase in muscle bulk (hypertrophy) resulting from strenuous exertion continued for years It is very difficult to decide this matter of hypertrophy In the first place it is very rare to obtain postmortem data in the case of vigorous athletes who while in normal health meet a sudden accidental death Secondly slight to moderate hypertrophy alone may occur during life but not be particularly obvious on examination even by roentgen study unless dilatation is also present Thirdly the range of the normal heart size is so great even in individuals of the same height weight and age that we have as yet no way of knowing whether or not in many cases there has been a change even when we determine the exact heart weight post mortem some more accurate correlation probably with body build than we possess at present is necessary as already stated in Chapter 2 before we can draw definite conclusions At present a very appreciable increase in size is possible in many cases without exceeding the outer normal limit Finally sufficient studies following the heart size of individual athletes or soldiers over many years have not yet been made Some observations have been reported which suggest that slight enlargement of the heart is more likely to be found in professional ski runners cyclists and oarsmen than in other athletes Also a few football players may have shown slight cardiac enlargement However even veteran marathon runners have failed to show enough hypertrophy to be evident by roentgen ray study Cardiac enlargement apparently largely dilatation found in some athletes during their period of intensive sport may subside when the athletic life is given up The immediate reaction of heart size to vigorous exercise in an athlete is usually a diminution as shown by roentgen ray study not to be accounted for entirely by a rapid heart rate

It appears likely from the data that we possess at present that most hearts can endure great physical strain without difficulty and without enlargement but that a few react differently and eventually increase in size It is quite possible that the chances of producing cardiac enlargement by physical strain

(the athletic heart) are greatest when four factors coincide (1) great *physical strain* (2) *rapid growth at adolescence* (3) *temporary or chronic* ill health as from respiratory infection or anemia and (4) unfavorable myocardial inheritance (to endure such strains) In most instances however the circulatory system including the heart can in youth and sometimes even at older ages be brought to a high degree of efficiency and stamina in athlete soldier and laborer alike by prolonged and skillful training

It is of considerable interest to note that the hearts of very active animals are much larger than are those of relatively inactive animals of the same size *for example the heart of the hare is three times as heavy* relative to body weight as that of the rabbit while the heart of the racing greyhound is in proportion to size the largest mammalian heart of all (Herrmann 1926) Finally when animals such as dogs or rats are made to exercise strenuously for long periods of time it is found that eventually their hearts are considerably larger and heavier than those of control animals of the same age and size and even from the same litter This is especially true when the strenuous exercise is imposed during the period of rapid growth There is no indication that such hypertrophy when it does occur is harmful Recent studies indicate that athletes do not suffer early disability or death because of their exercise in youth in fact the reverse seems to be the case at least as regards oarsmen (Cooper, et al 1937 Hartley and Llewellyn 1939) An interesting volume was published by Morgan in 1873 entitled University Oars a critical enquiry into the after health of the men who rowed in the Oxford and Cambridge Boat Race from the year 1829 to 1869 based on the personal experience of the rowers themselves these oarsmen lived longer and healthier lives than the average Britisher of their day Although it is true that it is the man of muscle (mesomorph) and therefore the athlete who is more prone than either ectomorph (thin) or endomorph (fat) to develop serious coronary heart disease in middle age (see Chapter 21) the oarsman is as a rule not built like the usually bulky mesomorph that is he is taller and more rangy and so may be less vulnerable to early coronary atherosclerosis Much more study of all types of athletes in this respect is needed

It is possible for a well trained athlete to support a valvular lesion like aortic regurgitation if not marked, without symptoms and be much more fit physically for the time being at least than a person living a sedentary life whose heart is undamaged In fact in the absence of important symptoms exercise in moderation is beneficial for a person with chronic heart disease at any age because of its favorable effect on the peripheral circulation (reducing venous stasis and the hazard of thrombosis) pulmonary reserve general musculature digestion nervous system and morale It is wise however in the long run to limit considerably the strain of vigorous exercise on the heart when there is clear evidence of enlargement with or without valvular disease especially during rapid growth in adolescence

Military service The problem of the selection of recruits for military service is a matter of recurrent interest and importance What has been said above in

the last section on the effect of work and exercise on the heart and circulation (as well as in the previous section on high altitude) has a direct bearing on this subject The other points of importance concern the incidence of cardiovascular defects found in the young men of any given community or country and the relative size of the army and navy and air force required When relatively small forces are needed the physical standards for acceptance of the recruits can be kept at a high and rigid level with only two classifications namely fitness for full combat duty and unqualified rejection Those accepted for service under these conditions should have no taint of suspected heart disease in the form of cardiac enlargement murmurs of valvular defects disturbing arrhythmias overhigh blood pressure or pulse rate or troublesome symptoms either of cardiac origin or of neurocirculatory asthenia nor should there have been a history of rheumatic fever pericarditis or coronary heart disease When however there is a large expansion of military forces the bars must be let down and not only the criteria for full combat duty made less rigid but also a third classification adopted namely of acceptance for limited service During preparations in this country for World War II about 20 per cent of the candidates for military service were rejected for physical reasons and about 8 per cent of the rejections were for cardiovascular defects ranking fifth in the list of causes for rejection after defects of teeth eyes nervous system and ears in that order The reasons for cardiovascular rejections varied greatly in different parts of the country but on the average ranged as follows in the order of frequency valvular disease hypertension neurocirculatory asthenia and tachycardia The chief difficulties concerned the upper limits of acceptable blood pressure and pulse rate the interpretation of a relatively slight apical systolic murmur and the detection of men likely to develop neurocirculatory asthenia under too little provocation more studies were considered necessary to solve these problems which concerned not only fitness for service at the moment but also the future state of health after the war should end (Levy Stroud and White 1943) A follow up study of men rejected during World War II for cardiovascular reasons has indicated that the only important problem that remains is that of the upper limits of acceptable blood pressure (White et al 1949)

After the recruit s admission to the armed forces his heart is likely to trouble him very little since presumably it is normal to start with He may acquire rheumatic fever and if he does he may have to be discharged from service not so much because of any heart disease that may result (unlikely if not already present before examination as a recruit) but rather because of prolonged illness and liability to recurrence Syphilitic aortitis with aneurysm or aortic regurgitation once the typical soldier s heart and responsible for half of all the cardiovascular deaths in the British Army in the middle of the nineteenth century (Myers 1870) has now been practically wiped out—only one death from aortic aneurysm occurred among 175 000 officers and men in the United States Army in 1937 Hypertension may develop among the older officers and men (Hillman Levy Stroud and White 1944) The other current difficulties

of the present day seem to be neurocirculatory asthenia and the discovery by symptoms or electrocardiogram, of presenile coronary heart disease (White 1941, 1951) Coronary heart disease was diagnosed in over 800 men under the age of 40 years in the army of the U S A during World War II, half of the diagnoses were confirmed by autopsy (Yater et al, 1948 see Chapter 21)

The problem of the airman s heart and circulation is a very special one As perfect as possible at the time of selection the aviator needs chiefly to avoid staleness and to keep himself fit so that, with the aid of oxygen, he may avoid the hazards of anoxia and of centrifugal forces in flights at high altitudes at high speeds and with sudden changes in speed and in direction Various tests especially the Schneider Index (see Chapter 10), have been instituted to measure the fitness of pilots and other aviators but not one of them is apparently as reliable as the close personal daily observation of the men by their own flight surgeon (Poppen 1941)

Pregnancy Pregnancy augments the blood flow and it has been estimated that the work of the heart increases steadily during pregnancy to a level of about 50 per cent above that in the nonpregnant state (Stander and Cadden 1932) it used to be thought that this maximum strain was at or just prior to full term but it has since been shown that it occurs toward the end of the ninth lunar month at which time lightening takes place following which there is much less strain on the heart and hence less failure in cardiac cases in the tenth month (Cohen and Thomson 1939) Another study has indicated that an important factor increasing the blood flow and the work of the heart in the pregnant state is the placental circulation the effects of which resemble those of an arteriovenous aneurysm (Burwell et al 1938) There has been a difference of opinion as to whether or not the heart is enlarged for the time being because of this increased work or increase in blood volume In advanced pregnancy it is difficult to judge the heart size because of the upward displacement of the heart by the enlarged uterus which displacement incidentally is responsible for prominence of the Q waves and inversion of the T waves in Lead 3 of the electrocardiogram so often found during the latter half of pregnancy There probably is slight enlargement in pregnancy, but it is clear that it is not great One other general observation of circulatory interest in pregnancy is that the enlarged uterus tends to obstruct the venous return to the heart and to cause stasis in the leg veins

Studies of pregnant women in this country have shown that about four per cent of all cases have heart symptoms or signs half of these have met by functional mitral systolic murmurs (probably associated with slight functional cardiac dilatation of little or no importance) or neurocirculatory asthenia the other half (2 per cent of all cases) have organic heart disease In some places Montreal for example a lower incidence of heart disease (1 per cent) has been found (Campbell 1923) in others it has apparently been much less (Schmidt in Bonn 0 4 per cent for example) and in others somewhat more (Daly in Chicago 2 8 per cent Schaupp in San Francisco 2 7 per

cent) More recent reports have given figures of 3 02 per cent (720 out of 23 858 pregnant women—Stromme and Kuder 1946) 3 2 per cent (203 cardiac cases of 6 285 consecutive pregnancies—Lesse, 1948) and 0 8 per cent (225 among 29 713 cases—MacRae 1948) The large majority of pregnant women with real heart disease have chronic rheumatic valvular defects mostly mitral disease with more or less stenosis Congenital defects syphilitic aortitis hypertension subacute bacterial endocarditis and thyrotoxicosis are relatively rare in pregnancy, making up altogether less than 10 per cent of the cases of heart disease in pregnancy Of the 225 cases noted by MacRae (1948) 91 5 per cent were rheumatic 5 8 per cent congenital and 2 7 per cent of other types

The important question concerning heart disease in pregnancy is the prognosis one of the most difficult problems in medicine Many patients even with considerable mitral stenosis go through pregnancy childbirth and the puerperium without any difficulty whatever and with no obvious injury to the heart although some authorities believe that even in such cases the strain eventually tells by shortening life This is a supposition difficult to prove because of the fact that persons with mitral stenosis usually live short lives anyway and are prone to heart accidents or failure even though not subjected to the strain of pregnancy Some cases even without evidence of much heart disease do badly because of the development of atrial fibrillation of recurrent rheumatic infection or of unexpected heart failure during pregnancy No rule can be set except that pregnancy should be forbidden or terminated early if symptoms and signs of heart failure appear early or if there have ever been such symptoms or signs the same advice applies when there are complications of atrial fibrillation free aortic regurgitation and hypertension It is particularly these conditions—atrial fibrillation heart failure marked aortic regurgitation and hypertension—that have been found by experienced observers to menace the lives of both mothers and infants Functional tests are of little or no importance in prognosis in comparison to the structural lesions that are found (Hamilton 1941) However even such conditions as marked mitral stenosis coronary thrombosis and heart block have not prevented normal pregnancy and delivery although it is certainly advisable to warn such patients against pregnancy except in the very rare case of uncomplicated congenital heart block Although the presence of heart disease of any type or severity always adds to the risk of pregnancy the chance may often be taken and even at moderate risk it may be justifiable to allow one pregnancy to occur and to continue if there is a great desire for a child One must remember incidentally that all the strain is not from the pregnancy and childbirth the care of the child after birth and of the growing family may be the cause of greater strain

Almost all the congenital cardiovascular defects have been represented among the successful cases except for those intensely cyanosed septal defects patent ductus arteriosus and aortic coarctation have not been a bar Even subacute bacterial endocarditis with penicillin during pregnancy has been successfully treated with living mother and child and uneventful pregnancies

have taken place in severely hypertensive women after successful reduction of their blood pressure by thoracolumbar sympathectomy

It is of the greatest importance to follow a cardiac patient through pregnancy with conscientious care and meticulous treatment This care has already proved invaluable and is the chief therapeutic and preventive measure In the nineteenth century the maternal mortality of pregnant cardiacs was almost 50 per cent (Zarday 1948) Hamilton (1941) has concluded that careful following of pregnant cardiac patients at the Boston Lying In Hospital has reduced the maternal mortality from about 12 per cent to less than 3 per cent in the past twenty years in his series of 1 000 pregnant cardiac patients, the first 500 showed a maternal mortality of 5 4 per cent and a fetal mortality of 18 0 per cent while the second 500 did considerably better with a maternal mortality of 2 6 per cent and a fetal mortality of 15 8 per cent The maternal death rate rose to 33 3 per cent in the presence of atrial fibrillation MacRae (1948) reported a maternal mortality of 3 1 per cent Lesse (1948) one of 1 5 per cent and Stromme and Kuder (1946) one of 1 3 per cent

If termination of pregnancy is essential the kind of anesthetic and type of operation (Cesarean section or delivery from below) are less important than the skill experience, and care of the anesthetist and operator Of a group of 74 cases of pregnancy with heart disease reported by Frey and Lardi (1938) all did well 43 being allowed to go to term with spontaneous childbirth 19 being operated on under local anesthesia by Cesarean section and 12 cases being interrupted early in pregnancy This record is very unusual generally a mortality of about 2 per cent is reported in pregnant cardiac patients One authority (Jensen 1927) believed that the difference of opinion expressed in the literature concerning heart disease and pregnancy is due to the inconsistency of comparing massed statistics from public or large hospitals with figures from the private practice of experienced obstetricians In general it is much better to allow patients to go to term and to deliver themselves (with help if necessary) than to interrupt pregnancy at an advanced stage It is also best to avoid Cesarean section

For the immediate treatment of heart failure in pregnancy the usual methods such as digitalis administration and diuretics are indicated but not termination of pregnancy at least until *after* the heart failure has been controlled *for auricular fibrillation digitalis quinidine or both should* be employed Apparently these drugs do not affect the fetus in a harmful way

Finally it is to be observed that the old tradition that the cardiac patient has a shorter or easier labor than the normal woman is not founded on fact (Nelson and Eades 1935)

Anesthesia and surgical operations Anesthetics and operative procedures do not cause heart disease although serious poisoning of the heart may occur from the effect of chloroform and abnormalities of the heart beat are common under anesthetics during operations Chloroform and the newer related anesthetic cyclopropane may produce premature beats paroxysmal tachycardia and in experimental animals ventricular fibrillation and death it is likely that

sudden death of patients during anesthesia by these agents comes in this same way, certainly they should be administered only by experts and never when the heart is already irritable or diseased General anesthesia with ether or ethylene and oxygen and local anesthesia are the procedures of choice from the cardiovascular standpoint During ordinary anesthesia premature beats paroxysmal atrial tachycardia and disturbance of the sinoatrial pacemaker have been noted by electrocardiographic study to be common they are generally only of passing interest although alarm may be occasioned temporarily by the very rapid pulse of paroxysmal tachycardia which subsides as a rule without leaving any trouble behind it and sometimes is dramatically banished by carotid sinus pressure Very rarely a paroxysm of tachycardia may be associated with a state of shock which proves fatal in such cases it is the very low blood pressure and not the rapid heart action that is the serious sign Anoxemia during anesthesia may produce temporary atrioventricular block. Spinal anesthesia is usually attended by a marked drop in blood pressure in the presence of hypertension or serious coronary heart disease spinal anesthesia should be avoided or undertaken cautiously

Patients with heart disease of nearly all types (rheumatic hypertensive coronary congenital thyrotoxic) go through anesthesia and surgical operations surprisingly well even with atrial fibrillation heart block or slight angina pectoris or congestive failure provided care is used But marked congestive failure very recent coronary thrombosis (that is within a few weeks) severe angina pectoris marked aortic stenosis and syphilitic aortitis add very appreciably to the operative risk sudden death being a common ending for all of these conditions operations of choice for example herniotomy interval appendectomy and often cholecystectomy and prostatectomy should be routinely avoided in such cases If there is time preoperative preparation of cardiac patients when indicated is usually helpful such as saturation with digitalis for congestive failure or atrial fibrillation except in rare cases however the presence of heart disease should not deter one from emergency operations In the presence of thyrotoxicosis congestive failure and atrial fibrillation may actually be cleared away by the operation itself (subtotal thyroidectomy) after suitable preparation with iodine (see Chapter 18) or by the newer use of irradiated iodine (see Chapters 21 and 30) It is also true that it is often wise to assume the risk of operation in cardiac patients for other conditions which are proving intolerable for life or comfort for example lumbodorsal splanchnic resection for severe hypertension in youth or middle age (see Chapter 19) and resection of the prostate gland for urinary obstruction (Mallory et al 1943)

In thoracic surgery routinely and when disturbing arrhythmias are present or threaten in other surgical fields protection of the patient by the administration of quinidine sulfate orally or parenterally (e g 0 2 to 0 4 gm 3 to 6 gr every 2 to 4 hours during the necessary period of time) may prove very helpful or even lifesaving

Collapse or death during anesthesia or surgical operation is rarely due to heart trouble it is almost invariably the result of shock from hemorrhage

infection trauma, or other cause, and the treatment of such collapse should not be directed at the heart but at the condition of shock hemorrhage or infection For cardiac standstill however, the heart should be massaged with the hand through the incised diaphragm if the abdomen is open or the thorax itself can be opened in the emergency if not already entered in the course of thoracic surgery Moreover if the heart is normal to start with epinephrine (adrenaline) chloride (solution of 1 to 1 000) may be injected within two or three minutes directly into the heart (0 25 to 0 5 cc) to restore a normal beat in some cases There have also been introduced devices to stimulate the heart to resume its beating or to abolish ventricular fibrillation by the use of electric shocks (Hyman, 1935, Beck 1941 and 1947)

Sufficient authentic recoveries by these procedures have by now (1951) been reported to make them advisable in every case of cardiac standstill during anesthesia the first method namely, that of massage is far preferable to the second since epinephrine may itself especially when applied directly to a diseased or irritable heart induce vent icular fibrillation and death The value of the massage combined with artificial respiration was demonstrated some years ago in a spectacular case of recovery at the Lahey Clinic 20 minutes after the heart had ceased its spontaneous beating (Adams and Hand 1942)

Postoperative complications may include so-called heart attacks or cardiac emergencies *in particular paroxysmal tachycardia* and paroxysmal atrial fibrillation and coronary thrombosis angina pectoris and acute pulmonary edema (with or without asthma) or other evidences of congestive heart failure are not common even in the presence of serious heart disease largely because the patients are having a regime of complete rest It is important when the cardiac reserve is low to avoid much saline solution by vein before or after operation since the extra sodium may precipitate pulmonary *or systemic congestion with edema Procaine in 0 1 per cent solution* intravenously has been helpful in dispelling bothersome ectopic tachycardia during surgical operations Disagreeable abdominal complications such as excessive intestinal gas may however precipitate heart trouble in those likely to have it More common postoperatively than serious cardiac conditions is the frequent complication of *pulmonary embolism* which may itself give rise to the acute cor pulmonale and be confused with coronary thrombosis or acute pulmonary *edema of cardiac origin (see Chapter 20), it demands search for* venous thrombosis in the legs and ligation of the thrombosed veins bilaterally since both legs are usually involved—this may be a lifesaving measure (see Chapter 28)

Excessive ingestion of food and fluid and salt *Overeating* may have so far as the heart is concerned a few untoward sequelae In the first place a state of obesity ill health and fatty infiltration of the heart may result from the excessive *ingestion of food and secondly heart failure* atrial fibrillation angina pectoris or acute coronary thrombosis may be precipitated by a hearty meal especially if followed at once by vigorous exertion or by horizontal recumbency This association between hearty eating and coronary thrombosis

or angina pectoris occasioned the one time erroneous diagnosis of rapidly fatal acute indigestion

Ingestion of excessive fluids and salt (sodium) It was long thought that the ingestion of excessive amounts of fluid daily for long periods of time might lead to cardiac enlargement and failure and the most typical example of such a state was called the beer heart It was reasonable to believe that the in creased work required of the heart to dispose of the enormously increased amount of fluid absorbed into the circulation by the copious beer drinking of former times (sometimes as much as 30 liters of beer a day were ingested routinely by champions in Munich) might lead to cardiac hypertrophy and dilatation (Bollinger 1884) however doubt was later cast on this idea by the fact that hypertension undoubtedly existed in many individuals but was unsuspected in the days before blood pressure measurements Occasionally large hearts are still found with no other explanation than that they are beer hearts However, evidence against the existence of the beer heart is the finding that ingestion of very large amounts of water (comparable to the vol ume of beer drunk by the champions of former days) by patients with diabetes insipidus does not apparently cause cardiac enlargement (Rowntree personal communication 1930)

The immediate effect of excessive fluid and salt (sodium) ingestion or injection is sometimes clearly seen as an injurious one in the case of a weakened heart or circulation It is known that temporarily the blood volume may be much increased by the ingestion of an excessive amount of fluid containing salt especially if the kidneys are slow to function In recent years when the forcing of fluids has been a common therapeutic procedure in the treatment of acute infection, and especially in the stimulation of kidney secretion and the washing out of kidneys and bladder in cases of prostatic hypertrophy before and after operation the strain on the heart and circulation of weakened patients has sometimes manifested itself by the development of dependent edema or by the precipitation of acute pulmonary edema (with or without cardiac asthma) or angina pectoris The intravenous injection of considerable amounts of normal saline solution (500 to 1 000 cc for example) has also on occasion been the cause of accidents because of the strain on the heart While the forcing of fluids continues rest digitalis and other such measures may prove ineffective It is usually a simple matter to establish a compromise between the surgeon and the physician in the matter of the amount of salt and fluid intake in a surgical patient subject to angina pectoris or congestive heart failure Glucose solutions may helpfully replace saline on occasion And in a cardiac patient acutely or chronically ill with congestive heart failure the one final measure that may lead to recovery temporary at least after other measures have failed is salt (sodium) restriction (See Chapter 30 and Bibliog raphy at end of this chapter)

Gastrointestinal diseases and disorders *Indigestion* aside from overeating which I have just discussed is related to heart disease in three ways (1) as an associated not a causative factor (2) as an irritating or aggravating factor

in the production of disorders of heart function whether the heart is normal or diseased and (3) as a cause of confusion in diagnosis Thus it is common for *spasm of esophagus or stomach (cardiospasm or pylorospasm) hiatus (diaphragmatic) hernia of the stomach, gallbladder disease (with or without stones) irritable or sluggish colon (with constipation) and much gas in stomach and intestines* (often consisting of swallowed air— cribbing) to be present in a person who has heart disease particularly of the hypertensive or coronary type This association is mainly an incidental one dependent primarily on two factors both common denominators namely (1) the aging process and (2) a type of individual or manner of life That a closer association does not exist is shown for example in the case of gallstones and coronary atherosclerosis of high degree which occur together twice as commonly as separately by the following facts (1) the former, gallbladder disease is more common in women while the latter coronary heart disease is more common in men and (2) the youngest cases of either condition are uncomplicated (Walsh et al 1941) Peptic ulcer is no more often found with heart disease than without it

The second connection between these various gastrointestinal disorders and heart trouble namely that of provocation of symptoms is an important practical problem and often demands careful study and skillful treatment. Extrasystoles paroxysmal tachycardia and even atrial fibrillation can be excited reflexly by gastrointestinal disorders even in a normal heart subsiding when the indigestion ceases Sometimes serious disorders of function angina pectoris and congestive failure can be prevented or relieved in a cardiac patient by straightening out the digestive trouble and from the standpoint of the sufferer from indigestion gastrointestinal symptoms may be relieved by correction of disorders of the circulation However radical measures of treatment such as cholecystectomy are not to be undertaken lightly hopin to get rid thereby of some such condition as angina pectoris Emergency operations may be justified but a cardiac patient may be made worse with the precipitation even of myocardial infarction or death by an operation of choice or convenience

Cirrhosis of the liver due to heart disease is uncommon Only 35 cases were found by Garvin (1943) among 790 consecutive adult autopsied patients who died of heart disease most commonly in those who had had chronic or recurrent congestive failure secondary to rheumatic heart disease (14 of 119 cases) or to hypertensive heart disease (14 of 264 cases) In my experience the more definite cases have been those with congestion due to mitral stenosis with or without tricuspid stenosis and chronic constrictive pericarditis but it is important to note that the liver may be engorged with blood and ascites may be present in such cases for a long time before any appreciable cirrhosis of the liver develops

Finally perhaps the most important relationship between heart trouble and indigestion is that of confusion in diagnosis often their symptoms re

semble each other closely particularly angina pectoris and the pain of cardiospasm on the one hand and the acute symptoms of myocardial infarction and gallstone colic on the other (see Chapter 21) the skill of the physician to distinguish them may be taxed to the utmost particularly when as so often happens both conditions cause symptoms in the same person and at the same time

Renal disease and uremia *Acute hemorrhagic nephritis* particularly in children may be accompanied by severe myocardial involvement with cardiac dilatation and even failure, which tend to subside as the nephritis clears (Ellis 1936 Master et al 1937 Langendorf and Pick 1938 Rubin and Rapoport 1938 Whitehill Longcope and Williams 1939) this is not hypertensive heart disease

Chronic nephritis has no direct bearing on the heart until renal insufficiency with *uremia* and potassium poisoning develop (see section on Poisoning) Nephrosis with edema and salt losing nephritis are important conditions which may complicate or indeed simulate cardiovascular disease and of course, chronic nephritis frequently complicates though it rarely initiates hypertensive disease

Collagen diseases and allergy There is an interesting and puzzling group of closely related diseases which involve the collagenous (connective) tissue of the body primarily often including that of the heart and which may be due to an allergic type of reaction One of these conditions is *disseminated lupus erythematosus* (diffuse collagen disease) which has attracted much attention of late in this disease of unknown cause polyserositis with pericarditis is common and there may be also endocarditis and myocardial involvement and even congestive failure *Polyarteritis (periarteritis) nodosa* is another rare but important disease of unknown origin sometimes attended by a high count of eosinophiles in the blood which also involves the viscera including the myocardium by causing a nodular reaction in the walls of the small arteries often leading to occlusion and local necroses (see Chapter 28) In the *Libman-Sacks syndrome* attended like the other two diseases mentioned above by skin manifestations in some of the cases there has been described an atypical verrucous endocarditis In some cases of *scleroderma* myocardial changes leading to fibrosis and failure have been found In *rheumatoid arthritis* also of unknown etiology pericarditis and endocarditis and myocarditis (even with partial heart block as shown by a long P R interval) may occasionally appear as complications not to be ascribed at least in most cases to a coincident rheumatic fever In a series of 45 autopsied cases of rheumatoid arthritis studied at the Massachusetts General Hospital 45 per cent showed involvement of the pericardium 17 per cent of the myocardium 20 per cent of the endocardium and 10 per cent of the aorta probably the result of the etiologic factor behind rheumatoid arthritis itself In several cases there were nodules in the pericardium and other tissues almost pathognomonic of the disease

Also a *serum carditis* and deleterious effects of *anaphylaxis* (allergy) on the myocardium have been described Electrocardiographic abnormalities are common in these various diseases How much all these different conditions (even including rheumatic fever) are related in etiology and especially in their effects on the heart and blood vessels we do not yet know but there does seem to be some sort of definite relationship which is further borne out by the favorable effect on nearly all these conditions at least pro tem by the new hormonal therapy with adrenocorticotropic hormone (ACTH) and cortisone

Miscellaneous conditions Before this part of the book is concluded there are various other cardiovascular relationships which though rare unim portant or poorly understood deserve mention Some of these were included in the long list of miscellaneous causes of minor abnormalities of the heart culled by von Bonsdorff from the records of the Boston City Hospital some years ago (1939) but there are still others of possible interest

Associated with acute hypertension in the *toxemias of pregnancy* (eclampsia) there may be serious toxic myocardial dilatation with acute heart failure and pulmonary edema The heart may dilate also in the severe stages of the toxic reaction to *burns* and *exfoliative dermatitis*

Polyserositis of high degree and long course and of unknown etiology is associated with a good many of the cases of chronic constrictive pericarditis a few of such cases are clearly due to tuberculosis but probably most of them are of that origin (see Chapter 27)

Amyloid sarcoid xanthomatous and *hemochromatous* myocardial lesions are uncommon but striking in their pathologic pictures They are of obscure origin difficult to diagnose and as a rule but a part of widespread systemic diseases *Amyloid disease* consists of the infiltration of various organs and tissues in the body especially spleen liver and kidney with amyloid, a glycoprotein the product as a rule of a long-continued wasting disease such as tuberculosis septic suppuration syphilis chronic arthritis anemia, and cancer the heart is not usually seriously affected but very rarely there may be so-called primary amyloid disease of the coronaries myocardium and *blood vessels with death from myocardial failure (Binford 1940) Sarcoid disease* or Boeck s sarcoidosis consists of a benign lymphogranulomatosis with hard tubercles composed of epithelioid cells surrounded by lymphocytes without caseation which involve various organs in the body but especially lymphoid tissue the etiology is unknown and the disease has often progressed extensively before it is discovered for it is usually symptomless at first the mediastinal glands and lungs and spleen are particularly the site of the lesions the myocardium and epicardium are sometimes involved but not as a rule to any important degree no cure is known but recovery is not uncommon *Xanthomatosis* consists of the infiltration of various tissues and organs of the body, including the skin and the heart itself with nodules or masses of cholesterol and cholesterol esters it is a complication of a disturbed metabolism of cholesterol fats often hereditary and is sometimes seen in diabetes

mellitus its chief importance so far as the heart is concerned is its association with serious and early coronary arterial atheromatosis which may lead to angina pectoris coronary occlusion with myocardial infarction and cardiac death *Hemochromatosis* may seriously involve the myocardium with deposition of iron in the muscle fibers and with resulting cardiac enlargement and failure and it may cause marked atrophy and pigmentation of the adrenal glands (Graef et al 1949)

Finally certain central and peripheral nervous diseases and abnormalities of skeletal musculature in function or in structure such as myasthenia gravis and progressive muscular dystrophy may be attended by heart muscle disease usually of mild degree while there remain a few mysterious cardiac diseases such as *Fiedler's acute isolated myocarditis* (see Chapter 25) and Davies endomyocardial necrosis and fibrosis (see Chapter 25)

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PART III

STRUCTURAL CARDIOVASCULAR ABNORMALITIES

CHAPTER 24

IMPORTANCE, DIAGNOSIS, AND INCIDENCE OF STRUCTURAL CARDIOVASCULAR ABNORMALITIES

In order to keep this volume within reasonable bounds in size which the addition of accounts of important new advances has already threatened to exceed it has proved possible to condense considerably certain portions of Part III in particular the chapters on Myocardial Disease and on Vascular Disease The reader is referred for further details to the sections on Pathology in the chapters of Part II of this book and to publications on pathology and on the peripheral circulation per se

The consideration of structural alterations in the heart and great vessels naturally follows a discussion of the fundamental causes that are responsible for them Although this pathologic field is important it is often neglected A generation and more ago it was the chief subject for discussion in heart disease and was much too predominant but then a vigorous reaction took place and the pendulum swung too far the other way interest became overwhelmingly centered on physiologic aspects of the circulation with a disregard of actual cardiovascular lesions A return to a study of structural pathology has been a healthy sign

Structural abnormalities of the heart affect often to a very important degree the mechanics and the functional state of the circulation Not only may high blood pressure infection endocrine deficiency anemia and blood chemical influences seriously affect the heart with little to be found structurally wrong with it unless the conditions are chronic but pathologic lesions alone in their turn too may cause serious cardiovascular strain as in the case of mitral stenosis aortic regurgitation myocardial infarcts and congenital defects We may find the cause of heart failure and death in one of these organic lesions just as we may find it in some condition entirely outside of the heart and great vessels It behooves us therefore to look for structural abnormalities in every cardiac patient as well as for evidence as to etiologic factors and as to the functional state of the circulation Such search is now routinely carried out by

the usual methods of examination which include inspection palpation auscul-
tation roentgenology and electrocardiography, and now cardiac catheteriza-
tion is also becoming routinely available to aid especially in the diagnosis of
certain abnormalities congenital and acquired by x ray visualization of the
catheter and by determination of the blood oxygen content and pressure in the
superior vena cava right atrium right ventricle and pulmonary artery (see
Chapters 10 and 13 in particular)

Much has appeared in the medical literature about mistakes in diagnosis in-
cluding the diagnosis of heart disease, and there have been various efforts to
correlate antemortem and postmortem diagnoses It has been shown that more
careful history taking and physical examination including more correct ap-
praisal of auscultatory findings as well as the use of other methods of study
like electrocardiography and roentgenology have in recent years reduced
greatly the errors of cardiovascular diagnosis, but there are likely to remain
some pathologic conditions that cannot be diagnosed clinically In other words
not only may errors arise from carelessness or incomplete study but errors
may also be due to the very fact that some structural abnormalities give rise
to no clinical symptoms or signs and so even under the most favorable cir-
cumstances are undiagnosable Such abnormalities include (1) acute or lesser
grades of chronic endocarditis involving valves or heart chambers with little or
no valvular deformity (2) lesser grades or earlier stages of coronary athero-
sclerosis and narrowing (3) slight aortic disease whether aortitis or athero-
matosis (4) relatively slight myocardial involvement consisting of hypertrophy
of muscle fibers or of degenerative or inflammatory changes and (5) acute
or chronic pericarditis of lesser degrees without friction rub or definite signs
of effusion enlargement compression or fixation of the heart Moreover
sometimes the very first attack of coronary insufficiency or the onset of acu
coronary thrombosis may be rapidly fatal

Errors of diagnosis may thus be divided into three groups first those that
are preventable because they are due to well marked lesions and should be
discovered if careful and complete examinations are made second those that
may or may not be preventable because the lesions are slight to moderate in
degree and sometimes give signs and sometimes do not and third those
that are so slight or cause so little strain that no signs ever result Most of
the diagnostic errors in cardiovascular disease when careful clinical work is
done fall into this last category and the clinician need feel no chagrin when
the pathologist discovers some slight lesion that could be of no clinical im-
portance or could give rise to no symptoms or signs

Since the clinical diagnosis of organic heart and aortic disease is based on
the finding of enlargement valvular lesions pericarditis aortic dilatation and
congenital defects (except in a few cases without these findings but with
angina pectoris or important abnormalities in cardiac function revealed by
electrocardiography) it may be said that about 2 per cent of the population
of much of the world show during life signs of organic heart disease through
the presence of structural cardiovascular abnormalities varying very much
with age from less than 1 per cent in childhood to 10 per cent or even much

iore in old age increasing with each added decade Many of such abnormalities are of little importance often of far less importance than symptoms ke angina pectoris in cases that happen to show no signs of structural defects At postmortem examination the pathologist finds that far more than 1 5 o 2 per cent of hearts or great vessels show abnormalities Most of these abnormalities are however small and unimportant and do not constitute real disease or else they are terminal and not diagnosable clinically Nearly half of ill cases examined post mortem at the Massachusetts General Hospital from 1896 to 1919 showed cardiovascular lesions (1 906 out of 4 000 autopsies) out these were often trifling (Cabot 1926)

Of patients actually seeking advice because of cardiac symptoms or signs he percentage of those with organic lesions that is structural abnormalities varies considerably in different groups for example from 22 per cent in a small group of cases noted in private practice (Cabot 1926) to 62 per cent in a larger group (1 000 cases) seen in consultation (White and Jones 1928) and 87 per cent in a group of 1 000 general hospital cases (White and Jones 1928) Since many individuals with symptoms or signs of cardiac nature never visit the hospitals but nevertheless are sufficiently bothered to consult their own private doctors the last figure is much too high to represent the average Cabot s series is too small to have any but suggestive value although it is quite likely that it is near the correct figure for the community at large including all individuals with cardiac symptoms or signs who do not bother to obtain medical advice Of the total of those cases who because of cardiac symptoms or signs do visit doctor or hospital the intermediate figure of 50 per cent probably represents reasonably well the number who have organic heart disease

Of the various abnormalities enlargement of the heart is by far the most common with valvular disease next and aortic disease pericarditis and congenital defects less frequent Of a series of 1 846 cases with cardiovascular lesions found at postmortem examination at the Massachusetts General Hospital Cabot reported that 1 209 (65 5 per cent) were recognized by the pathologist as having some enlargement of the heart (Cabot 1926) in many of those who showed no enlargement in this series the lesions were too trivial to be dignified by the term disease Myocardial infarcts were recorded in only 26 cases (1 3 per cent) acute in 20 Valvular defects (but not necessarily deformity sufficient to cause either regurgitation or stenosis) were present in 21 per cent of 1 230 autopsied cases of Cabot s cardiac series including latent as well as manifest lesions Pericarditis was present as an acute often terminal condition in 9 8 per cent of 1 906 cases of his series and as a chronic often silent condition in 6 per cent more while syphilitic aortitis was found in 5 per cent aneurysms in 2 per cent and congenital defects in 1 5 per cent In comparison among the last 100 cases with significant cardiovascular lesions autopsied at the Massachusetts General Hospital (September 1949) there were 70 cases with cardiac enlargement, 47 cases of myocardial infarction (16 acute 31 chronic) 26 cases of valvular defects (7 mitral alone 4 aortic alone 15 both 0 tricuspid) 5 cases of acute pericarditis 7

cases of chronic pericarditis, 3 cases of syphilitic aortitis 0 cases of aortic aneurysms (dissecting in 0) and 3 cases of congenital defects

Of a series of 1 000 clinical cases of organic heart disease in northeastern United States Dublin reported (1925) that 88 per cent showed cardiac enlargement, 44 per cent mitral stenosis 15 per cent aortic insufficiency, 3 per cent aortic stenosis 17 per cent aortitis and 1+ per cent aneurysms Of another clinical series of 2,314 cases of organic heart disease in New England 47 per cent showed valvular disease, 4 per cent syphilitic aortitis 3 per cent pericarditis 2 per cent congenital defects 0 5 per cent aneurysms and the large majority showed definite cardiac enlargement (White and Jones 1928) this series included many private patients living in an enlightened community and had much less syphilis than the other groups cited a state of affairs still more evident now with the passage of time—at present far fewer than 1 per cent of my own private patients have syphilis even as a latent condition

The pathologic lesions found in cases of sudden death are also of especial interest In one series of 198 individuals (Bedford 1933) organic heart disease was found in 122 (62 per cent) of whom 81 per cent were males and 19 per cent females Nonvalvular disease (87 cases) was over twice as common as valvular disease (35 cases) Atherosclerosis of the coronary arteries of an important degree was present in 63 cases (57 males and 6 females) in 33 patients there was gross myocardial fibrosis with definite infarction in 27 and in 6 rupture of the heart wall had occurred at the apex of the left ventricle Gross fatty infiltration of the heart was found in 2 females The aortic valve alone was diseased in 20 cases the mitral valve alone in 7 and both in 8 An aneurysm of the aorta was found in 22 cases of the dissecting *variety* in 2 Syphilitic aortitis involving the coronary artery mouths occurred in 13 cases

In another series of 130 cases of sudden death (Munck 1931) 74 (57 per cent) showed well marked coronary artery disease and 33 (25 per cent) had syphilitic aortitis

In two of the largest series of autopsied cases of sudden death there were the following findings (1) 2 000 in number (Martland 1940), organic heart or aortic disease was found in 1 590 (79 5 per cent) 1 115 of which were of coronary or hypertensive type 262 syphilitic 116 rheumatic while 731 showed extensive coronary artery disease of which 304 had acute thrombosis and (2) 2 030 in number (Helpern and Rabson 1945), cardiovascular disease in 89 per cent of which more than half were coronary cases (see Chapter 34 for further details)

Of some special interest is a recent analysis of the postmortem findings at the Massachusetts General Hospital and Boston City Hospital (Medalia and White 1951) of individuals dying at the age of 50 years or more This gives some idea of the expected findings in older people The following were the incidences of the ' underlying and contributing causes of death in both males and females (Table 11)

A report has just been published from the Geriatric Clinic of the Peter Bent Brigham Hospital in Boston entitled *Diseases in Old Age A Clinical and Pathological Study of 7 941 Individuals Over 61 Years of Age* (Monroe

Table 11

THE PREVALENCE OF UNDERLYING AND CONTRIBUTING CAUSES OF DEATH AFTER THE AGE OF 50 IN 1 251 INDIVIDUALS AT THE MASSACHUSETTS GENERAL AND BOSTON CITY HOSPITALS

	6th Decade	*7th Decade*	*8th Decade*	*9th Decade*
Totals	313	340	286	312
Coronary sclerosis	144	224	222	262
Atherosclerosis including coronary sclerosis	215	243	251	305
Nephrosclerosis	71	107	111	171
Cerebrovascular lesions	32	31	43	68
Bronchopneumonia	81	116	105	147
Liver and gallbladder disease	44	84	68	81
Cancer	68	83	85	67
Tuberculosis	39	30	34	14
Gastric and duodenal ulcers	25	20	26	21

1951) Clinically only 44 6 per cent of the patients in this series had no heart disease but the pathologists found a much smaller fraction than that for only 28 5 per cent of the men and 28 3 per cent of the women had normal hearts out of 1 177 autopsies The heart weights at autopsy were compared In the normal men 61 to 85 years old the heart weights ranged from 302 to 373 gm while in the normal women of the same age the weights ranged from 274 to 304 gm In the cases of valvular heart disease the average weight of the heart in old men was 549 gm and in old women 439 gm Finally the heart weight in cases of nonvalvular disease averaged 526 gm in old men and 426 gm in old women when there was coronary artery occlusion and 493 gm in the old men and 394 gm in the women without coronary artery occlusion

In all this discussion of structural changes in the heart and great vessels it is of the utmost importance to recognize the wide range of the normal a range which has not yet been adequately determined and the very wideness of which makes it difficult or impossible to identify slight abnormalities For a full discussion of the range of the normal heart the reader is referred to Chapter 2 and for certain normal measurements to Table 12 which appears at the end of this chapter One particular measurement as an example may be appropriately referred to here namely that of heart weight

The normal heart weight bears a fairly definite relation to body weight 0 40 to 0 45 per cent but ranging from 0 35 to 0 50 per cent lower values being found more often in women and obese individuals and higher values in men and thin persons The normal heart weight may be calculated from the body weight with an error up to about 10 per cent The weight of the heart in the normal adult male averages about 300 gm and in the female about 250 gm The limits of the normal range of weight of the adult heart are 200 and 350 gm Heart weight has been related also to body length (Zeek 1942) Heart volume and certain other measurements are to be found in Table 12

Table 12

NORMAL ANATOMIC CARDIAC MEASUREMENTS

WEIGHT (gm)

Adult	
Range	200–350
Average male	300
Average female	250
Percentage of body weight (Smith)	
male	0.43%
female	0.40%

Child (Vierordt Muller)	
Birth	20– 25
1 month	15– 20
6 months	20– 25
1 year	30– 40
2 years	45– 55
4 years	65– 75
8 years	95–105
12–16 years	150–250

Left ventricle right ventricle
Birth 1:1
Adult
Range 1.71:1 to 1.95:1
Average 1.85:1

Individual chambers (adult)	
Left ventricle	130
Right ventricle	70
Left atrium	24
Right atrium	25

VOLUME AND CAPACITY (cc)

Heart tissue (Beneke)	
Birth to 3 months	20– 25
1 year	30– 35
6 years	65– 75
10 years	110
15 years	130–175
Adult	210–290

Capacity of chambers in adult (average) (Hochrein)	
Right atrium	163
Right ventricle	137
Left atrium	140
Left ventricle	121
Total (4 chambers)	561

Thus the *total volume of the filled heart* averages 811 cc (561 + 250) from these figures *during life* the heart volume is never so great since all four chambers are not full at the same time—this would mean a subtraction of about 200 cc from the volume stated above leaving approximately 600 cc

OTHER MEASUREMENTS (adult)

Ventricular wall thickness (midway between base and apex and not including papillary muscles)	
Left	10–12 mm
Right	3– 4 mm
Ventricular septum	9–12 mm

Valve circumferences (cm)	
Tricuspid (Average 12)	11–13
Mitral (Average 10)	9–11
Pulmonary	8–9
Aortic	7– 8

Valve areas (sq mm) (Creutzfeldt)	
Tricuspid	[illegible]100
Mitral	1,600
(Dexter et al.)—During life	
Mitral	4,000–6,000

Heart length (longitudinal diameter in cm) (Average 11 cm)	10–12
Heart width (transverse diameter in cm) (Average 9 cm)	8–10
Heart depth (anteroposterior diameter in cm) (Average 7 cm)	6– 8

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CHAPTER 25

MYOCARDIAL DISEASE
CARDIAC ENLARGEMENT HYPERTROPHY AND DILATATION
MYOCARDITIS

The myocardium is the most important part of the heart If it is sound a great deal of disease of endocardium and pericardium and great vessels of valvular deformities and septal defects and of strain from hypertension can be endured for a surprising number of years if it is seriously diseased or fails death may come quickly even though all the rest of the cardiovascular system is perfect

Myocardial disease includes various abnormalities The most common are hypertrophy and dilatation (due fundamentally to the strain of greatly increased work) and the degeneration and fibrosis due to coronary insufficiency Less frequent are inflammatory changes or true myocarditis atrophy toxic and malnutritional changes fatty degeneration from severe anemia fatty infiltration congenital defects neoplasms and traumatic lesions

Dilatation of the heart chambers is a very common condition occurring sometimes as a compensatory reaction to valvular disease and sometimes as a natural sequence of a failing heart muscle under the effect of the conditions which cause myocardial disease itself

Enlargement of the heart, which includes both hypertrophy of muscle and dilatation of chambers will be considered first since it is by far the most common of all cardiac abnormalities

CARDIAC ENLARGEMENT HYPERTROPHY AND DILATATION

Cardiac enlargement is the commonest and most important evidence of heart disease *Often it can be taken as an index of the degree of cardiac strain*, since a very large heart indicates a great cardiovascular burden and an unfavorable prognosis while a small heart indicates a small degree of cardiac strain and a favorable prognosis except in the presence of serious coronary

disease It is to be noted at the outset that very important heart or aortic dis ease may be present with little or no enlargement examples of this are occa sional cases of syphilitic aortitis of angina pectoris and of coronary narrowing leading shortly to thrombosis with cardiac infarction Usually however a diseased heart is enlarged and its increase in size can be made out in many cases by clinical study alone although roentgenologic control is often invaluable

Enlargement of the heart may be due to hypertrophy dilatation or both The combination in varying degrees is much commoner than either condition alone except for very slight hypertrophy discoverable only at autopsy It is the dilatation rather than the hypertrophy that accounts for most of the in crease in volume especially of the largest hearts In fact hypertrophy alone or with little dilatation may increase the heart size extraordinarily little and in early stages is not discoverable clinically as in the case of many patients with hypertension A preponderant muscle weight increase gives rise to the so-called concentric hypertrophy of the heart When in the course of time the heart begins to fail and grossly to dilate or when there is a constant demand for an increased output as in aortic regurgitation the hypertrophy is associated with dilatation and is then called eccentric Another factor influencing the so-called concentric and eccentric types of hypertrophy is the state of the heart muscle at the time of death and at the postmortem examination if the heart stops in systole (contracted) the appearance of concentric hypertrophy is increased if in diastole (dilated) the appearance of eccentric hypertrophy is increased

Enlargement of the heart up to a weight of 425 gm may exist in a big man without clinical signs but hypertrophy of the heart beyond that weight should be found by clinical study Dilatation occurs as an important secondary factor if dilatation is absent slight cardiac hypertrophy may exist with no clinical evidence thereof except on occasion when studies are carried out serially by x ray or precordial electrocardiography, if dilatation is present the heart may be obviously enlarged clinically with little or no hypertrophy as in some cases of acute dilatation following acute coronary thrombosis with myocardial infarction

The cause of cardiac enlargement is heart strain whether intrinsic that is due to valvular disease myocardial infarction or true myocarditis (as in acute rheumatic fever) or extrinsic due to hypertension chronic thyrotoxicosis or severe anemia The strain may be acute or chronic overwhelming or slight The speed of enlargement of the heart and the preponderance of hypertrophy or of dilatation appear to depend in part on these factors of time and degree A quick occlusion of a large coronary artery may result in rapid cardiac en largement due to dilatation with the development of hypertrophy on recovery On the other hand hyperpiesia (essential hypertension) slowly beginning causes only gradual enlargement hardly to be made out on clinical examina tion and consisting primarily of hypertrophy the dilatation appearing later when the heart begins to fail and to enlarge more rapidly Mitral stenosis simi

larly acts slowly on the heart size involving the right ventricle instead of the left

The most common factors of heart strain giving rise to enlargement of the heart are hypertension of the essential type valvular disease of rheumatic or syphilitic origin and myocardial infarction Even in New England where rheumatic heart disease is the commonest of all clinical types producing cardiac symptoms and signs cardiac enlargement is more often found at postmortem examination without than with valvular disease

Less common causes of cardiac enlargement than hypertension and valvular disease are true myocarditis (especially during a severe rheumatic infection in childhood) cardiac infarction from severe coronary disease thyrotoxicosis chronic pulmonary disease (extensive fibrosis as in silicosis) and congenital defects Rare causes are arteriovenous aneurysms severe anemia beriberi hypothyroidism (myxedema) thoracic and spinal deformities chronic pericarditis with external adhesions and cardiac neoplasms Finally cardiac enlargement is occasionally of unknown cause undoubtedly there exist causes of enlargement still unrecognized or poorly understood A few possible factors not yet clearly recognized as causes of cardiac enlargement are as follows a severe infection rheumatic or otherwise may cause so much myocardial damage that the heart dilates and does not recover sufficiently to return to its normal size whether the valves are damaged or not excessively severe or prolonged physical strain as in athletic sports may rarely in the case of a sensitive heart produce some permanent cardiac enlargement prolonged and excessive tachycardia in certain arrhythmias (especially atrial flutter and fibrillation) may be to blame in a minority of patients so afflicted but particularly in infants a rare case of congenital idiopathic cardiac hypertrophy of lesser degree may survive to adolescence or adult life a combination of two or more of these factors is the most probable of all Therefore it is unwise as yet to label every large heart of unknown type hypertensive without more proof

Hypertrophy Hypertrophy consists of the increase in size of the individual muscle fibers and apparently not in their increase in number at least in adults although MacMahon (1937) has reported finding in infants and children a true active proliferation of the heart (with mitotic nuclear division) and regeneration of the myocardium following severe injury A comparative study has been reported of the size of muscle fibers seen in a normal heart weighing 300 gm in a hypertrophied heart weighing 500 gm and in an atrophied heart weighing 165 gm The ratio of muscle fiber size was 5 9 4 respectively (Karsner, Saphir and Todd 1925) An important feature of myocardial hypertrophy after maturity is the apparent failure of the blood supply to parallel in its growth that of the muscle fibers the ratio of one capillary to one muscle fiber in the adult remains throughout life no matter how large the heart becomes resulting in a relative coronary insufficiency in an enlarged heart compared to the normal (Roberts and Wearn 1941)

Whether the increased work and strain alone are primarily responsible or whether the hypertrophy is the reaction to trauma of the muscle fibers and primary dilatation due to the strain as has been suggested we do not know but we are aware of the fact that increase of the bulk and weight of the myocardium commonly follows considerably increased work if long sustained and that it occurs in the part of the heart primarily involved Although the heart is made up of complex masses of muscle continuous between the ventricles and between the atria respectively hypertrophy and enlargement may be very limited in location as in the case of left ventricular hypertrophy in hyperpiesia and of right ventricular hypertrophy in pulmonary valve stenosis When other factors like congestive failure appear the enlargement spreads to involve other parts of the heart for example, a failing hypertensive heart with functional mitral regurgitation shows secondarily enlargement of left atrium and of right ventricle Although it is common in the end stages of heart disease and failure or in combined strains to find general enlargement of the whole heart it is important to recognize that at first the enlargement may be entirely limited to one heart chamber sometimes with slight atrophy of another and that such limited enlargement may persist for years or that it may always preponderate A discussion of the factors responsible for enlargement of the individual heart chambers will begin on page 650 All of the muscle of the heart wall of any given chamber whether atrial or ventricular (and including the papillary muscles) apparently takes part in the hypertrophy Finally it is important to realize that a structurally sound hypertrophied heart muscle may dilate and fail even though the muscle cells show no degeneration post mortem

In 1910 Bernheim introduced the concept of right ventricular obstruction and failure secondary to marked bulging of the septum into its cavity in cases of gross hypertrophy of the left ventricle However the adaptability of the eccentric right ventricle to such a heart shape and the rarity of convincing proof have caused a debate as to the existence of such an entity (Evans and White 1948 Russek and Zohman 1950 Wilson and Zimmerman 1950)

Dilatation Dilatation of the heart is a very common condition frequently occurring along with hypertrophy as a part of cardiac enlargement It consists of a stretching of the heart wall due to a weakening or atonic state of the muscle or to a response to the physiologic demand for an increased output of blood per beat (as in exercise or in compensation for valvular regurgitation or anemia) If the cause of such acute dilatation ceases the heart regains its usual size unless the injury has been irreparable Often the dilatation persists or increases with continuance of the strain the tone of the muscle may partly recover but a permanent stretching of the fibers may persist In some instances enlargement of the heart due preponderantly to dilatation may decrease clearly under observation as in occasional cases of acute or subacute rheumatic carditis during convalescence occasional cases of congestive failure from any

cause under treatment with rest and digitalis cases of anemia under specific therapy, some cases of hypertensive heart disease treated by thoracolumbar sympathectomy and cases of the myxedema heart under thyroid therapy

Hypertrophy and dilatation The largest hearts are usually the heaviest hearts since hypertrophy and dilatation are almost invariably associated and when a heart is so large that it reaches almost to the chest wall on the left and considerably over halfway to that on the right it will be found in the adult to weigh from 500 to 1 000 gm

A few instances occur in which a single chamber is much dilated this is almost always the left atrium which in cases of mitral valve deformity with atrial fibrillation may become enormous large enough to hold a liter and a half of fluid or more and to fill a large part of the thoracic cavity extending across the mediastinal space to the right as well as to the left The left atrium may be much larger than all the rest of the heart, which is attached to the atrium like an appendage the term 'aneurysm of the atrium has been applied to such cases Both atria may be greatly increased in volume as shown in Figures 120 121 and 122 The enlargement is almost wholly due to a stretching of the atrial wall but the muscle is somewhat thickened also The largest left atrium on record is said to have had a capacity of 3 liters (Minkowski 1904) I have encountered one holding 1 760 cc (Figures 121 and 122), there are records of two other left atria larger than this 2½ liters (Muller 1905) and 2 liters (Goedel 1929)

The heaviest heart—cor bovinum found with marked aortic regurgitation or stenosis or extreme hypertension of long standing—may weigh as much as 1 000 gm over three times the normal The heaviest heart recorded is said to have weighed 58½ oz (1 755 gm) and showed aortic and mitral valvular disease and a moderate degree of adhesive pericarditis of rheumatic origin in a man 28 years old (Smith 1850) the heart referred to above with the enormous left atrium pictured in Figures 121 and 122 weighed 850 gm and showed well marked but not extreme mitral stenosis and regurgitation and very slight aortic stenosis

Preponderant enlargement of either ventricle tends to give a rather characteristic shape to the heart *like an egg with blunt end at the* base of the heart in the case of a large left ventricle and more spherical in the case of a large right ventricle The more hypertrophy and the less dilatation there are in left ventricular enlargement the more the heart shape resembles that of preponderant right ventricular enlargement, the more the dilatation of the left ventricle the longer is the heart

The factors responsible for enlargement of the left ventricle are as follows for hypertrophy with little or no gross dilatation uncomplicated chronic hypertension is mostly responsible and aortic stenosis occasionally (Figure 123 page 654) for dilatation with little or no hypertrophy there are serious acute myocarditis as in some cases of rheumatic fever and diphtheria acute myocardial infarction of large size acute high grade anemia and severe trauma for hypertrophy and dilatation we may blame aortic regurgitation mitral regurgitation

chronic high grade anemia rarely chronic adhesive pericarditis and most often left ventricular failure complicating chronic hypertension aortic stenosis, and myocardial infarction from acute coronary occlusion



FIG 120 Roentgenogram of thorax showing enormous heart shadow in a case of chronic rheumatic heart disease with mitral and tricuspid stenosis Male P W age 35 Note that the right heart border touches the right border of the thorax

The factors responsible for enlargement of the right ventricle are as follows for hypertrophy with little or no gross dilatation the most common cause is failure of the left ventricle without failure of the right an occasional cause is mitral stenosis and rare causes are extensive pulmonary fibrosis pulmonary endarteritis and congenital pulmonary stenosis (Figure 124 page 655) for dilatation with little or no hypertrophy we may find serious acute myocarditis as in some cases of rheumatic fever and diphtheria acute high grade anemia severe trauma and acute massive obstruction in the pulmonary circulation from pulmonary embolism (acute cor pulmonale) for hypertrophy and dila tation right ventricular failure complicating left ventricular failure is most

FIG 121 Photograph showing marked enlargement of the heart due to dilatation of left atrium right atrium and right ventricle in a young man with mitral stenosis and regurgitation and atrial fibrillation The volume of the filled heart was 4 600 cc its weight empty was 850 gm and the chambers had the following capacity left atrium 1 760 cc right atrium 650 cc right ventricle 330 cc and left ventricle 70 cc Anterior view A heart model of normal size is shown for comparison The arrow points to the interventricular sulcus LA = left atrium LV = left ventricle RA = right atrium RV = right ventricle (A full description of this exceptionally large heart was published in the *J.A.M.A* 1931 XCVI 840)

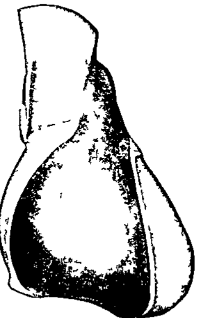






FIG 122 Right lateral (*A*) and left lateral (*B*) views of heart shown in Figure 121 Note backward bulging of the left atrium best seen in the left lateral view LA = left atrium RA = right atrium LV = left ventricle RV = right ventricle

commonly the cause with mitral stenosis pulmonary stenosis and the chronic cor pulmonale as occasional factors and less often tricuspid valve disease chronic high grade anemia chronic severe thyrotoxicosis, congenital idiopathic hypertrophy and pulmonary regurgitation

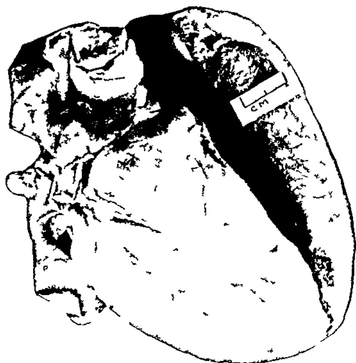


FIG 123 Photograph showing a heart with a much hypertrophied left ventricle (in a case of aortic stenosis) The left ventricular wall measured 2 cm in thickness (normally 1 0 to 1 2 cm)

It is evident that several factors act simultaneously on both ventricles to cause acute dilatation and chronic dilatation and hypertrophy but uncomplicated hypertrophy of either ventricle is independent of the other when hypertrophy of the right ventricle follows hypertrophy of the left ventricle there is always an essential element of dilatation of the left ventricle as a part of the sequence

Enlargement of the left atrium is chiefly the result of dilatation and occurs most markedly with mitral valve disease but also often with failure of the left ventricle Similarly *enlargement of the right atrium* is chiefly due to dilatation and results from tricuspid valve disease or much more commonly from failure of the right ventricle

Finally interesting but rare types of general cardiac enlargement are those found in infancy and once called congenital idiopathic hypertrophy Cases of glycogen storage (von Gierke s) disease (von Gierke 1929 Pompe 1933) of myocarditis *of unknown cause of coronary anomalies and of excessively*

rapid rates in paroxysmal tachycardia (Hubbard 1941) have lately been separated out leaving only a minority now unexplained The heart weights in these various conditions are often several times the normal (Figure 74 page 324) and the prognosis is bad except in the cases of tachycardia which re cover when properly treated

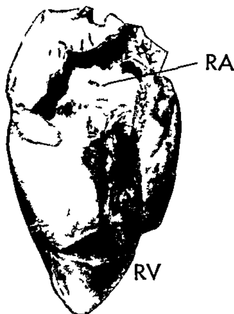


FIG 174 Photograph showing marked right ventricular hypertrophy in chronic cor pulmonale M C male age 29 Three years after beginning of exposure to silica dust in gritty-soap factory Death due to complicating pneumonia RA = right atrium RV = right ventricle (Kindness of Oxford University Press chapter by P D White on Cor Pulmonale)

MYOCARDIAL DEGENERATION AND FIBROSIS CARDIAC RUPTURE CARDIAC ANEURYSM CALCIFICATION

Myocardial degeneration and fibrosis result chiefly from extensive coronary atherosclerosis with obstruction to the blood supply of the myocardium If the deficiency is gradual in its progress so is the myocardial change which begins as scattered or local fatty degeneration and necrosis and ends in re placement of a certain number of muscle fibers by connective tissue (fibrosis) or in some slight degree of regeneration of muscle if the blood supply is soon enough re-established by collateral circulation If the deficiency is abrupt and extensive in the amount of muscle involved an infarct results which may heal as a firm scar (see Figures 106A 106B and 107 pages 532 533 and 535) or may proceed to aneurysm or rupture of the heart wall

Myocardial necrosis and fibrosis can also result from other causes than coronary atherosclerosis though less commonly Syphilitic or embolic (chiefly

by bacterial vegetations) occlusion of the coronary mouths and high degrees of aortic stenosis also may rarely produce such lesions, three cases of myocardial infarction due to syphilitic stenosis of the coronary ostia among 6 225 consecutive autopsies in New Orleans have been recently reported (Burch and Winsor 1942) Disseminated areas of ischemic necrosis may result from carbon monoxide poisoning or very severe anemia (Friedberg and Horn 1939), and Davies (1948) has described endomyocardial necrosis and fibrosis in Africans

Cardiac aneurysm and rupture long recognized pathologically have only in recent years been properly attributed in the great majority of cases to coronary thrombosis with myocardial infarction Both cardiac aneurysm and rupture are as a rule only postmortem findings unrecognized for the most part before autopsy although they have been diagnosed in an increasing number of cases of late especially cardiac aneurysm by the aid of roentgenology (Figure 125)

Rupture of the heart usually occurs a few days after acute myocardial infarction sets in due to friability of the heart wall Among 25 000 autopsies at the Los Angeles County Hospital from 1924 to 1941 there were 865 cases of unhealed myocardial infarction 72 of these (or 8 per cent) showed cardiac rupture 13 involving the septum (Edmondson and Hoxie 1942) the threat of such an accident is a very potent reason for insistence on absolute rest during the first fortnight after acute coronary occlusion In a series of 22 mentally ill patients with acute myocardial infarction 20 of which were clinically undiagnosed and hence untreated rupture of the heart caused death in 16 (73 per cent) (Jetter and White 1944) in contrast to the average findings of 5 to 10 per cent in the wards of a general hospital as further exemplified by a series of 10 cases of cardiac rupture (9 5 per cent) among 105 patients with acute myocardial infarction (Friedman and White 1944) Rupture rarely if ever occurs in cases of chronic or healed myocardial infarction it was found in none of 165 such cases in Friedman and White's series. It takes place within the first two weeks of the infarction most commonly at the end of the first week. Cardiac rupture usually ends in instantaneous death *but in some cases when the tear in the wall is small and the intrapericardial* leak of blood gradual death may be postponed for hours finally resulting from hemopericardial tamponade (see Chapter 27) unless relieved by paracentesis not a likely procedure in such cases Cardiac rupture may rarely result from gumma pyogenic abscess tuberculous lesion echinococcus cyst malignancy and trauma Rupture of papillary muscles and interventricular septum may also occur spontaneously in fresh myocardial infarction

Cardiac aneurysm in slight degree is very common in fact it is present in nearly every case of extensive myocardial infarction When aneurysms of the heart were first described several centuries ago they referred to general enlargement of the heart or of its chambers but in recent years the term has been reserved for local pouches or sacs in the heart wall The cardiac aneurysm begins as an acute lesion and if no rupture occurs it becomes chronic with little or no danger of rupture after the first fortnight it varies in size from a

slight bulge of the wall to an enormous cavity as large as the rest of the heart Sometimes it contains a thrombus which may send off emboli The aneurysm is located as a rule either on the anterior and left wall of the left ventricle near the apex frequently involving a bit of the lower part of the interventricular septum (Figure 106A page 532) or on the posterior wall of the left ventricle high up These two sites are the usual locations of cardiac infarcts due most commonly to occlusion of the descending branch of the left coronary artery in the one case and to occlusion of the right coronary artery or the circumflex branch of the left in the other case Other but rare locations of cardiac aneurysms are the upper part of the interventricular septum where the aneurysm may be also of congenital origin and the outer wall of the right ventricle Most

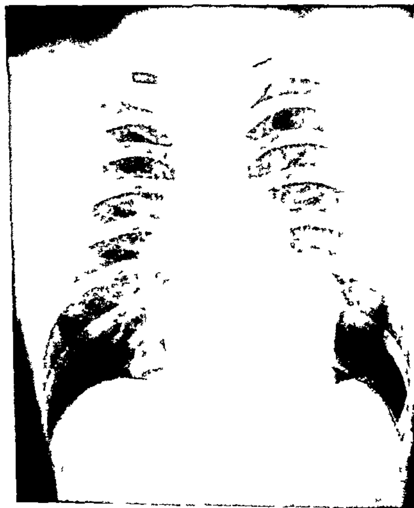


FIG 125 Roentgenogram of thorax showing cardiac aneurysm consequent to myocardial infarction H O D., male age 39 (Kindness of Dr A N Ferguson Fort Wayne Ind)

cardiac aneurysms are small or shallow and undiagnosable in life the largest ones are easily diagnosed by roentgen ray, appearing as a bulge at the left border of the heart above the apex in the usual anteroposterior view and showing often an alarming but apparently benign degree of expansile pulsation during systole (Figure 125 page 657)

Marked dilatation of either atrium especially of the left has been called aneurysmal but this is a general and not a localized enlargement Aneurysmal pockets in valve cusps and sinuses of Valsalva have also been described due usually to bacterial endocarditis and rarely to congenital defects There is no special treatment for cardiac or valvular aneurysms except that strain on the heart should be carefully limited

The deposition of lime salts in the heart muscle (calcification) is occasionally found chiefly where there has already been myocardial disease particularly degeneration following infarction from coronary closure There is a disturbed local metabolism in such cases as there is at the base of the heart valves at times and in chronic valvular lesions with calcification of the cusps in whole or in part The lime salts are most often found in the papillary muscles of the left ventricle or in the septum or anterior wall near the apex of the left ventricle Irregular areas of calcification occur varying in size from that of a pea to that of a walnut They may cast a shadow by roentgen ray which distinguishes them from the heart muscle about them A cardiac aneurysm may be outlined roentgenologically by calcification of its wall In very rare cases actual bone is found instead of mere masses of lime salts

MYOCARDITIS

Myocarditis or true inflammation of the myocardium occurs in rheumatic fever and in severe cases of diphtheria infrequently in cardiovascular syphilis and rarely in other infections like virus and rickettsial diseases (except in scrub typhus tsutsugamushu fever when it is more common), typhoid fever tuberculosis trichiniasis trypanosomiasis, hydatid disease and pyemia (see Chapters 14, 16 and 17) it can be diagnosed clinically only by the realization of the frequency of mild to moderate involvement of the myocardium in these infections and in a few cases circumstantially by the finding of acute heart block abnormal electrocardiograms or acute cardiac dilatation without definite valvular lesions coronary disease or hypertension to account for the dilatation In an analysis of 1 402 cases of myocarditis diagnosed post mortem Gore and Saphir (1947) have presented a number of interesting ratios of the incidence of this condition in various diseases Some of these ratios where more or less adequate numbers of cases were involved are as follows myocarditis was found in 144 of 221 cases of diphtheria 5 of 135 cases of malaria 9 of 581 cases of tuberculosis 2 of 66 cases of syphilis 5 of 41 cases of schistosomiasis 1 of 400 cases of epidemic hepatitis 32 of 222 cases of virus pneumonia 13 of 144 cases of acute encephalitis 13 of 94 cases of poliomyelitis, 11 of 48 cases of coccidioidomycosis 1 of 16 cases of tularemia, 14

of 160 cases of acute glomerulonephritis, 7 of 44 cases of exfoliative dermatitis and 3 of 12 cases of Boeck s sarcoid The discussion of the various etiologic types of myocarditis has been included in detail in appropriate chapters in Part II of this book

There are in addition three kinds of myocarditis of unknown cause one occurring in earliest infancy in fact probably in fetal life to give rise to one type of congenital cardiac hypertrophy (Kugel and Stoloff 1933) a second called Fiedler s isolated myocarditis and acute interstitial myocarditis of rare and obscure nature with tendency to sudden death to be further discussed below and a third also obscure and rare occurring in variable degree in adults with cardiac enlargement which leads to congestive failure or sudden death (Levy and von Glahn 1937) Whether or not these three groups are related as varying results of the same underlying condition is not known

The clinical diagnosis of myocarditis so freely used in the past has wrongly included many other conditions in particular the frequent instances of hypertensive heart disease in which there is cardiac hypertrophy and enlargement but no inflammatory reaction in the muscle the term myocarditis has also wrongly included frequent instances of coronary heart disease in which degenerative changes fibrosis and atrophy may occur without actual inflammatory process In the attempt to diagnose heart disease more accurately the term myocarditis is wisely being abandoned in large part we must remember nevertheless that there does exist such a condition as myocarditis which is in particular exemplified by involvement by rheumatic fever and diphtheria

FIEDLER S MYOCARDITIS

In 1899 there was published in the *Festschrift zur Feier des funfzigjahrigen Bestehens des Stadtkrankenhauses zu Dresden Friedrichstadt* a paper of sixteen pages entitled Ueber akute interstitielle Myokarditis (Concerning Acute Interstitial Myocarditis) by Dr A Fiedler chief physician to the City Hospital at Dresden Quotations from this interesting paper are as follows (translation by myself)

> Based on the clinical records and autopsy findings of four cases who died and on the record of an additional patient who survived the disease there has been presented herewith the description of an acute inflammation of the myocardium generally coming on very abruptly and with a chill which is almost certainly of microparasitic origin
>
> This disease attacks as a rule young people and runs its course with little or no fever The pulse rate is almost always very much accelerated and very rarely reduced The heart is dilated both to right and to left The heart action is irregular and dyspnea cyanosis evidences of stasis in both greater and lesser circulations and a great tendency to heart weakness are constantly present.
>
> I cannot convince myself that we are dealing in these cases with an ordinary septic infection To my mind it is much more evident that a microorganism differ

ent from the usual agents producing sepsis is responsible localized directly in the heart muscle and setting up there an inflammatory reaction or that a poison is produced which reaches the heart by the blood stream and affects particularly the interfibrillary tissue of the myocardium

In diphtheria, scarlet fever and exanthematic typhus that is in diseases which are caused by entirely different infectious agents and which differ also so widely in their clinical manifestations we find, as mentioned above interstitial myocardial changes very similar to those in the cases which I have observed and described herein

We may conclude that in all these different diseases one and the same poison does not produce these myocardial changes but that entirely different infectious agents are present which cause this inflammation either directly or indirectly

I would not fail to mention that even though interstitial myocarditis is always preponderant this designation is not to be accepted in the strictest and exclusive sense of the word The interstitial changes in the muscular tissue were the first and most important but as microscopic investigation showed there was also always present a parenchymatous inflammation too consisting of slight changes in the muscle fibres themselves

And now still a few words about the prognosis of the disease in question as mentioned above our cases ended as a rule fatally This does not however force the conclusion that all of these cases have a bad prognosis

Microscopic sections of the myocardium in those cases who survived only a few days after the onset of chill and serious illness showed invasion of the myocardium with small round cells and beginning disintegration of the myocardial fibers

Therefore the designation of this disease as purely interstitial (or isolated) is misleading One might better term it acute myocarditis of unknown cause although there is no reason why one may not add Fiedler s type' in parenthesis after such a description It is quite possible that an acute fulminating virus myocarditis may be the answer If the etiologic factor is evident it should be so stated and the designation Fiedler s omitted In time all such cases may be separated off from the one time useful eponym

ATROPHY OF THE HEART MICROCARDIA

Atrophy may be dismissed with two observations (1) When relative disuse or inanition or Addison s disease is responsible for the atrophy the heart actually decreases somewhat in bulk and weight in whole or in part with slight decrease in size of the muscle fibers such atrophy is infrequent and slight in most cases Atrophy is sometimes seen in the left ventricle in well marked mitral stenosis and in the whole heart in a few cases of chronic constrictive pericarditis and in bedridden patients as in chronic tuberculosis Marked *atrophy of the left ventricle has been produced in the experimental* animal by an artificial tricuspid valve lesion (Stadler 1907) (2) If degeneration or inflammation causes local atrophy partial fibrosis results but the heart as a

whole does not decrease in size or weight if it must still keep up an active circulation in fact there may develop a compensatory hypertrophy

True microcardia if it exists must be very rare it has been reported as a congenital anomaly at birth but further confirmation is necessary

TOXIC AND MALNUTRITIONAL MYOCARDIAL CHANGES

In rare cases there are myocardial changes of noninfectious toxic origin and others associated with malnutrition and avitaminosis (see Chapter 23) Chloroform carbon monoxide benzol and the toxins of eclampsia and uremia have been noted as factors responsible for focal necroses and severe malnutrition with vitamin deficiency as in beriberi and rachitis has occasionally caused myocardial degeneration and edema with dilatation of the heart Upon specific therapy both the general malnutritional edema and the cardiac dilatation tend to subside it is thought that in especially severe cases in children congestive heart failure may supervene to cause death (Waring Charleston S C personal communication 1936) In scorbutus hemorrhages may occur throughout the heart As a matter of fact avitaminosis tends to be multiple and therefore to show multiple effects both generally and in the heart

Sensitivity to the sulfonamides has also been reported as a cause of damage to the myocardium which may be reversible (Lilienfeld et al 1950 Mayer and Levy 1950)

FATTY DEGENERATION IN SEVERE ANEMIA

Associated with the cardiac dilatation and hypertrophy that result from severe anemia there is a characteristic fatty degeneration of certain parts of the heart muscle farthest removed from the arterial ends of the capillaries giving rise to a curious striped appearance which has occasioned the term tiger or tiger lily heart Otherwise fatty degeneration is but a part of the effect of severe infections like diphtheria or of infarction due to serious coronary disease

FATTY INFILTRATION

Fatty infiltration of the myocardium especially involving the right ventricle is a definite entity most common in middle aged and elderly women In extreme cases the wall of the right ventricle is found largely composed of layers of fat infiltrated between the muscle bands In rare cases this condition has been blamed as the primary or secondary cause of heart failure When excessive it may be merely a part of generalized fatty infiltration in other organs and throughout the body

AMYLOID DISEASE XANTHOMA HEMOCHROMATOSIS SARCOIDOSIS

Rare affections of the myocardium of obscure origin include amyloid disease xanthoma hemachromatosis and sarcoidosis which tend to be but part

of a general process of amyloid xanthomatous and iron deposition and sar coid infiltration throughout the body (see Chapter 23) When such processes have become evident elsewhere, as for example in the skin and the heart is en larged or in other respects abnormal showing for instance otherwise unex plained heart block by electrocardiogram it is reasonable to suspect that these diseases have involved the heart

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SEE ALSO REFERENCES IN CHAPTERS 7 CARDIOVASCULAR ROENTGENOLOGY 9 ELECTROCARDIOGRAPHY 13 CONGENITAL CARDIOVASCULAR DEFECTS 14 RHEUMATIC HEART DISEASE 15 BACTERIAL ENDOCARDITIS 16 CARDIOVASCULAR SYPHILIS 17 OTHER INFECTIONS 21 CORONARY HEART DISEASE AND CORONARY OCCLUSION AND 23 OTHER ETIOLOGIC FACTORS AND RELATIONSHIPS

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CHAPTER 26

ENDOCARDIAL AND VALVULAR DISEASE INTRACARDIAC THROMBOSIS

Endocardial disease is chiefly a matter of endocarditis but it includes also infarction (incident to coronary thrombosis) atheroma neoplasm and trauma of the endocardium

ENDOCARDITIS

Endocarditis or inflammation of the endocardium is made up of several types varying according to the etiologic factors These etiologic types have been described in detail in Chapters 14 15 16 and 17 of this book and will be but briefly summarized here They are the "rheumatic" subacute bacterial acute bacterial terminal verrucose syphilitic tuberculous and other infectious types

The *rheumatic endocardial involvement* is a simple verrucose lesion with rows of small vegetations or thrombi consisting mostly of fibrin on the valves often located only along the line of closure of the mitral cusps but sometimes situated on other heart valves also where they close (Figure 83 page 362) on the chordae tendineae and on the atrial mural endocardium Recovery may be *complete* without deformity and with but little thickening of the valve leaflets but *more* often there is extensive scarring with contraction and adhesion of the cusps and of the chordae tendineae causing stenosis and regurgitation especially after repeated rheumatic infections This type of acute endocarditis is rare before the age of 5 years and relatively uncommon after 15

The *subacute bacterial endocardial involvement* consists primarily of a lesion of the valves with larger vegetations than in the case of rheumatic endo carditis and with more extensive infection of the mural endocardium of atria and of ventricles due to extension of the process from the valves or to contact with infected cusps (Figure 88 page 393) The vegetations contain masses of bacteria usually streptococci of the viridans type or products of their degenera tion Chronic healed scarring and deformity are now the rule *in* subacute bac terial endocarditis because of the lowered mortality from this disease by the use of penicillin in the active stage Rupture of valve cusps and chordae

tendineae occasionally occurs, and embolism from the endocardial vegetations is very common This type of endocarditis is commonest between the ages of 18 and 35 years but may occur at any age thereafter or less commonly earlier

The *acute bacterial endocarditis* is much like the subacute bacterial type except that it is a more fulminating process and now becoming rare It is caused by any one of a variety of organisms, most commonly by streptococcus pneumococcus staphylococcus or gonococcus

Terminal verrucose endocarditis resembles the rheumatic type It is quite common as a complication of many fatal illnesses It is probable that a non rheumatic verrucose endocarditis can occur in many patients who recover leaving slightly thickened cusps difficult to distinguish from very mild chronic rheumatic endocarditis but of that we have not yet clear proof

Syphilitic involvement of the endocardium is due to an extension of syphilitic aortitis to the aortic valve causing an adhesion of the cusp ends against the aortic wall which results primarily in a widening of the commissures and secondarily thereby in aortic regurgitation It should be noted however that the wall of the very first portion of the ascending aorta may be so weakened by the syphilitic process that it dilates and that therefore this dilatation rather than aortic valvular disease may be responsible for some of the widening of the aortic valve commissures and of the resultant aortic regurgitation Further extension of the syphilitic process from the aortic valve may slightly involve the anterior cusp of the mitral valve

Tuberculous endocarditis consists of the involvement of the endocardium by military tubercles with or without ulceration It is rare

Also rare are other infections like actinomycosis and extension to the endocardium of myocardial abscesses

Combined lesions are frequently found and it is sometimes possible to determine in the pathologic specimens the effect of each individual factor

OTHER ABNORMALITIES OF THE ENDOCARDIUM

Other abnormalities of the endocardium include a variety of conditions Frequently there are unimportant *atheromatous* lesions of the valvular or nonvalvular (mural) endocardium which are similar to areas with early fatty changes in the aorta and coronary arteries but the endocardial lesions progress only rarely to clacified plaques In some cases with extensive subendocardial calcification the endocardium may be eroded by direct pressure Occasionally the destructive process associated with myocardial infarction from coronary thrombosis or embolism penetrates to the endocardium to cause ulceration and intracardiac thrombosis over the site of the ulceration *Mural thrombosis* may however and probably most commonly does develop as the result of stasis rather than of endocardial injury especially in a fibrillating atrium or in a ventricular (as in an aortic) aneurysm *Neoplasm* and *trauma* of the endocardium are rare (see Chapter 23) as are also *congenital valvular defects* (see Chapter 13) *Diffuse parietal endocardial sclerosis* occurs in rare cases most

commonly in congenital heart disease its pathogenesis is still obscure *Endocardial and subendocardial calcification* is however very frequent and consists of two types the more common being superimposed on old valvular disease mainly rheumatic and the other (Monckeberg s sclerosis) being an independent atherosclerotic process which attacks especially the valve rings and bases but may also invade the cusps It is important to note that chronic endocarditis with extensive valvular deformity may exist even in old age with little or no calcification and that much calcification may occur with little or no evidence of antecedent endocarditis although both processes are to be sure frequently combined the old endocardial scarring doubtless favoring the calcification An interesting very rare dark brown pigmentation (ochronosis) of heart valves aorta cartilage and bone has been ascribed to an inborn fault of tyrosin metabolism (Neumann Brno 1946) Finally *endocardial fibrosis* of unknown origin has been described in Africans by Davies (1948)

VALVULAR DISEASE OF THE HEART

Valvular disease of the heart is an important subject for consideration not only because it is often the primary cause of heart failure but also because there is much unnecessary confusion associated with it in the medical literature and in the minds of many physicians As noted in Chapter 14 valvular disease is a common structural abnormality wherever the rheumatic infection is frequent it must however be distinguished from valvular incompetence due to cardiac dilatation alone

Valvular disease is caused by acute infection which includes the rheumatic (most commonly) subacute bacterial acute bacterial and terminal verrucose types by syphilitic invasion and rarely by tuberculosis it is sometimes due also to atheromatous and sclerotic changes often with calcification chiefly at the base of the aortic valve without any evidence of infection uncommonly it is due to congenital malformation rarely it is due to trauma either direct or indirect There may be an acute fulminating or terminal involvement or the process may be very chronic consisting of a healed after-effect of some acute process that occurred many years before Often two factors are combined for example subacute bacterial endocarditis superimposed on congenital defects or on chronic rheumatic valvular disease calcification of valves already deformed by infection or rupture of inflamed valves

Valvular disease may be so slight that there is not enough deformity to interfere in any way with the valve function in such cases there may be an entire absence of signs and symptoms On the other hand the valvular defect may be so great that it is itself the cause of much cardiac enlargement and failure Even with objective signs of valvular deformity there may be no disability and life may extend to a ripe old age as in the case of Dr Herman F Vickery who lived to be nearly 84 with a moderate degree of rheumatic mitral stenosis in addition to some coronary insufficiency (White and Bland 1941) A coincidence of coronary heart disease and chronic rheumatic heart

disease is more common than generally recognized (Gardner and White 1949)

It is important always to distinguish between the influence of active disease and that of structural abnormality on the circulation and health For example acute bacterial endocarditis may show but little valve deformity and yet terminate fatally in a short time because of the toxic effect of the infection or of embolism while chronic mitral stenosis or aortic regurgitation of rheumatic origin though of high degree may allow many years of life with a badly crippled heart An abnormal valve no matter how slight its deformity is always of some significance because it is a point of less resistance to infection or strain than is a normal valve and sometimes it is but a part of some important acute or chronic disease These facts are frequently lost sight of in the casual disregard of valvular disease which has been common in the past

Clinically it is often difficult or even impossible to say whether valvular insufficiency is due to disease of the valve itself or to cardiac dilatation with normal valve or to cardiac dilatation plus valvular disease Sometimes it is easy to make the differentiation but in certain cases especially in those with advanced heart failure we may utilize without avail all methods of study including percussion auscultation sphygmomanometry roentgenology and graphic methods In most cases of advanced heart failure it matters little whether the valves are diseased or not so far as prognosis and treatment are concerned It is in the earlier cases without congestive failure and with relatively little cardiac enlargement that the differentiation between valvular disease and functional defect alone is much more important and is often possible All methods of examination are sometimes needed in this differentiation one method alone like auscultation or roentgenology may be misleading

Of the four heart valves the mitral is the one most commonly affected it is damaged in well over half of all cases of valvular disease Aortic valve disease is next in frequency followed by lesions of the tricuspid valve, which is but rarely deformed to any important extent The pulmonary valve is very infrequently involved In a series of 208 cases of valvular disease in New England examined macroscopically post mortem the mitral valve was found diseased in 85 6 per cent the aortic valve in 44 7 per cent the tricuspid valve in 15 9 per cent and the pulmonary valve in 1 9 per cent (Cabot, 1926) The aortic and mitral valves were involved together in 19 2 per cent the aortic mitral and tricuspid in 11 per cent the mitral and tricuspid in 2 9 per cent the pulmonary and tricuspid in 1 per cent and all four valves in 1 per cent In a postmortem series of 126 cases of valvular disease studied in Vienna the percentages of disease of mitral aortic tricuspid and pulmonary valves were 60 76 25 and 0 respectively (Kaufmann 1927) but these patients were all male adults and syphilis accounted for one third of the aortic valve lesions In a series of 300 autopsied cases of valvular heart disease in Berlin (Sperling 1872) the mitral valve was involved in 85 per cent of all cases and in 52 per cent without other valves affected the aortic valve was involved in 43 per cent altogether and alone in 13 per cent the tricuspid valve in 10 per cent altogether but

alone in only 1 per cent while the pulmonary valve was diseased in only 1 per cent of the total cases and in no case alone In a series of 1 097 cases in New England in which valvular disease was sufficient or definite enough to be diagnosed clinically 56 3 per cent were thought to have mitral valve disease alone 14 7 per cent aortic alone and 28 9 per cent both aortic and mitral rare cases were thought to have tricuspid valve disease along with mitral disease or with mitral and aortic but in no case of the series was tricuspid valve disease a certainty pulmonary valve disease was diagnosed in no case (White and Jones 1928) In a clinical series of 1 781 cases of valvular disease at the Johns Hopkins Hospital (Hirschfelder 1918) mitral valve disease alone was diagnosed in 51 per cent aortic valve disease alone in 22 per cent and both together in 20 per cent Why the mitral valve should be most often involved and why the left heart valves are more frequently diseased than those on the right side is not clear Greater vascularity of the mitral valve has been suggested as a cause but it is probable that the greater force of closure of the mitral and aortic valves allows more readily a lesion produced by direct or indirect bacterial action combined with trauma at their lines of closure than in the case of the right heart valves which are under less pressure except in fetal life when the pulmonary and tricuspid valves are more often involved than the aortic and mitral valves

The characteristics of the individual valve lesions will now be considered in the order of frequency of valvular involvement mitral aortic tricuspid and pulmonary

A MITRAL VALVE DISEASE

Disease of the mitral valve is common but it is frequently diagnosed when not present because a systolic murmur at the cardiac apex due to cardiac dilatation is wrongly interpreted as due to valvular disease

Etiology *Cause* Mitral disease is due in the large majority of cases to rheumatic infection It may be found either in the acute stage or as a chronic lesion In the acute stage the rheumatic infection may not be recognized as such either because it gives very obscure or indefinite signs or because no doctor is called at the time or because the doctor who is called is unfamiliar with atypical rheumatism but the resulting heart involvement is generally regarded as rheumatic and is called the rheumatic type probably justifiably It is possible that other infections especially of focal nature may be sometimes responsible but this still remains to be proved Subacute and acute bacterial endocarditis are much less frequent causes of mitral disease and until lately were always fatal Terminal verrucose endocarditis as a complication is not infrequently found in patients who have died from all kinds of diseases it involves the mitral valve most commonly Atheromatous lesions in the mitral valve are very similar to early atheromatous lesions of the blood vessels they consist of the infiltration and precipitation of lipoids cholesterin crystals and calcium in the leaflets on their ventricular sides suggesting the

importance of mechanical factors (Hellwig 1942) Sclerotic change with calcification at the base of the valve sometimes fixing the annulus as a solid stony ring is infrequently encountered when calcification involves the mitral valve leaflets themselves it is almost invariably superimposed upon antecedent rheumatic mitral stenosis in which case it may further deform the valve sometimes with masses of calcium projecting into heart chambers or even into the atrioventricular ostium to increase the degree of stenosis Tuberculous and syphilitic involvement are very rare as is also congenital deformity in the nature of either stenosis or atresia

Age Mitral valve disease is commonly found in youth and middle age, it is less common in old age although both the rheumatic and the sclerotic types are found in old persons in infancy mitral valve disease is very rare

Sex The female sex shows a higher percentage of mitral valve disease than does the male in about the ratio of three to two

Pathology Although the pathology of endocardial disease whether of inflammatory atherosclerotic or traumatic nature has already been discussed in the earlier part of this chapter and in Chapters 14 15 and 16 the particular pathology of chronic mitral disease needs brief consideration The healing of acute endocarditis may leave no defect in valve function and merely a slight thickening of the valve cusps along their lines of closure With marked or repeated inflammation the damage is greater and the contracting scar tissue may cause all grades of deformity Two processes in particular are responsible for defective function one of these is fusion of the cusps at their commissures causing both stenosis (narrowing of the ostium or opening) and regurgitation (leaking back of the blood stream through the incompetent valve), the other is fusion of the chordae tendineae with shortening which is equally important in deforming the valve In very chronic cases after repeated infections the fusion of the cusps is so pronounced that there is simply a diaphragm or funnel with a narrow ostium in the place where the freely acting mitral cusps should be (Figure 126) The small opening varies in shape and size and it has received a variety of names such as buttonhole and fish mouth Occasionally the damaged valve becomes calcified and absolutely rigid with stony surface exposed to the blood stream through erosion of the endocardium A few instances occur in which a valve cusp is rent or a chorda tendinea torn off its attachment at one end so that the torn fragments float freely at one end or edge in the blood stream The valve ring at its base and sometimes the valve cusps themselves to a greater or lesser extent may become calcified and fixed with more or less stenosis Large vegetations in bacterial endocarditis may sometimes produce a virtual mitral stenosis without actual valve deformity Finally developmental defects and probably infectious lesions may give rise in the fetus to stenosis hypoplasia or even atresia of the mitral valve

Mitral regurgitation and mitral stenosis are almost invariably combined pathologically In rare instances however they may be considered pure (1) when retraction of the relatively undamaged or at least relatively nonadherent valve cusps is caused by shortened contracted and perhaps fused



FIG 176 Photograph showing marked stenosis of the mitral ostium with fish mouth valve and relative tricuspid insufficiency Note thick wall of left atrium (Kindness of Dr Ronald Grant Guys Hospital London)

chordae tendineae giving rise to mitral regurgitation without stenosis and (2) when the valve cusps are fused giving rise to mitral stenosis without sufficient fibrosis or thickening of the cusp extremities or shortening of the chordae tendineae to allow regurgitation When the valve opening is rigidly fixed with fibrous or calcified edge in marked mitral stenosis a certain amount of regurgitation necessarily occurs too Clinically, preponderant mitral stenosis produces a different picture from that of preponderant mitral regurgitation and when the two defects are about balanced the clinical findings show the combined effects of moderate mitral stenosis and moderate mitral regurgitation From the pathologic point of view it would be more accurate to make a clinical diagnosis of mitral disease with preponderant stenosis or "with preponderant regurgitation but the shorter terms mitral stenosis and mitral regurgitation are much simpler for use and sufficiently accurate if we realize that they refer to the clinical results of preponderant defects of the mitral valve

Functional mitral insufficiency due to left ventricular dilatation should not be regarded as a trivial condition Often the left ventricular dilatation is the result of serious myocardial disease itself of infarction for example or of left ventricular failure due to the strain of hypertension or of myocardial insufficiency because of serious anemia it may be due to adhesive pericarditis or it may be a compensatory mechanism with aortic regurgitation It is possible that the displacement downward of the papillary muscles as the result of the ventricular dilatation is a more important factor in causing the mitral regurgitation than is dilatation of the atrioventricular ostium that is of the valve ring The chordae tendineae are of limited length and with their attachments to the papillary muscles moved away from the base of the heart their insertions on the valve cusps are likewise displaced downward This results in an inability of the mitral cusps to close tightly no matter how tautly the chordae may stretch or how normal or elastic the cusps may be regurgitation of greater or lesser degree follows Occasionally in fact frequently factors due both to left ventricular dilatation and to deformities of valve cusps and chordae tendineae combine to cause mitral regurgitation

Functional mitral stenosis occurs (a) occasionally as a relative stenosis with normal mitral valve but marked left ventricular dilatation (b) in very rare instances of tumor or thrombus in the left atrium large and free enough to obstruct to a variable degree the blood flow through the mitral valve from atrium to ventricle and (c) perhaps to a slight degree in marked aortic regurgitation when the aortic regurgitant blood stream forces back the anterior cusp of the mitral valve

The average normal circumference of the mitral valve in the adult human heart is 10 cm (ranging from 9 to 11 cm) a circumference less than 7 5 cm may be considered to indicate definite stenosis The area of the normal adult mitral ostium has a range during life of 4 to 6 sq cm An area of 1 sq cm or less is found in the case of marked mitral stenosis (Gorlin and Haynes 1950)

Effects of mitral valve disease on the heart If the mitral valve lesion results primarily in stenosis the left atrium and right ventricle bear the brunt of the burden the former becoming hypertrophied and dilated and the latter hyper trophied at first and finally dilated also when the strain is much increased Eventually the right atrium also is involved with dilatation and hypertrophy after the right ventricular dilatation has resulted in more or less constant tricuspid regurgitation The left ventricle may remain practically unaffected even when the right ventricle and left atrium become double their normal size in fact the left ventricle may be a little smaller than normal The cardiac apex is sometimes formed in large part by the right ventricle

If on the other hand regurgitation is the chief defect the left ventricle becomes involved as well as the left atrium and right ventricle Hypertrophy and dilatation of left ventricle and left atrium and hypertrophy of the right ventricle are the primary effects with dilatation of both right heart chambers later With marked and chronic mitral regurgitation the heart may become enormous all four chambers being involved Functional mitral regurgita tion will naturally have the same effect on the heart chambers as organic mitral regurgitation of the same degree and chronicity but with functional mitral regurgitation other factors such as heart failure may cause death before enough time has elapsed to duplicate the picture found with organic mitral disease without failure at the onset or recovery from the dilatation and failure (due to anemia or other factors responsible for the functional mitral regurgitation) may permit the valve again to become competent

Since both defects—stenosis and regurgitation—are generally combined to a greater or lesser degree in cases of organic mitral disease the effects on the heart depend in part on the relative amounts of stenosis and regurgitation and in part on the absolute degree of the valvular disease With slight mitral regurgitation or stenosis there is scarcely any heart burden and but little change in heart size but when either stenosis or regurgitation is extreme the changes are marked

High grades of organic mitral stenosis are much more common than are high grades of organic mitral regurgitation and are doubtless better borne The development of mitral stenosis is a gradual one the earliest defect in rheumatic children being more regurgitant than stenotic It requires at least two years as a rule for the establishment of mitral stenosis Mitral murmurs heard during the first year after the onset of a moderate or severe rheumatic infection in a child are to be attributed to dilatation of the left ventricle in cident to the rheumatic myocarditis and not to mitral valve deformity (Bland White and Jones 1935) such murmurs may eventually merge into those of mitral valve disease or they may disappear occasionally when recovery is especially satisfactory (Bland Jones and White 1936) The heart and body as a whole gradually develop compensatory mechanisms to take care of the strain of the stenosis often for many years The rather sudden onset of functional mitral regurgitation with heart failure or its more gradual develop

ment with marked aortic regurgitation may however be a great additional burden for the heart and hasten its failure before a compensatory mechanism can be established

A particular finding occasionally seen in mitral disease is an enormous enlargement of the left atrium It is not alone the degree of stenosis that accounts for such cases but rather the combined effect of mitral regurgitation mitral stenosis the dilatation that comes with atrial fibrillation acute rheumatic involvement of the myocardium of the left atrium, and other factors not well understood perhaps an active circulation or sometimes pericardial adhesions over the left atrium In a series of 26 cases of very large left atria found at autopsy at the Massachusetts General Hospital 16 showed mitral stenosis and 10 mitral valve deformity (causing regurgitation) without stenosis which indicates that structural mitral regurgitation is by no means an innocuous condition

The heart muscle in mitral valve disease may be normal except for hypertrophy With acute endocarditis there are often acute inflammatory myocardial reactions like the Aschoff bodies in the rheumatic infection but with chronic healed valvular disease there need not be any trace of previous infection in the perfectly healthy muscle Eventually the myocardium may become exhausted and fail without evidence of pathologic change unless there is a complication such as acute rheumatic infection or serious coronary disease Thus it is at times the valve lesion and not myocardial disease that eventually causes failure and death although it is equally true that active infection especially recurrent rheumatism or some other complication proves too great a burden for the heart that is already overloaded In recent years there has been too great a tendency to blame the heart muscle entirely and to exonerate the valve lesion This is a limited point of view although it has been helpful in calling attention to the fact that mitral insufficiency is often the result of heart failure or dilatation and not its cause In the process of this demonstration the pendulum has swung too far The truth rests between the extreme points of view

The effects of mitral valve disease on organs of the body other than the heart vary with the degree of involvement of the valve and with the occurrence of complications The only direct effect is on the pulmonary circulation which becomes engorged, the small arteries and capillaries are seriously affected with marked dilatation and thickened walls resulting in great difficulty in the transfer of oxygen and carbon dioxide from the limited inspired air to blood stream and vice versa (Parker and Weiss 1936) There develops a steadily increasing pulmonary arterial pressure when either stenosis or regurgitation of the mitral valve is at all pronounced All this leads naturally to a diminution in air space and vital capacity and to a tendency to bleeding or effusion of serum (edema) into the interstitial tissue and into alveoli and bronchioles there slowly develops also an extensive interstitial fibrosis with enormous thickening of the alveolar walls to resemble eventually the picture of "malignant pulmonary sclerosis due to other causes Also in time in cases of

chronic mitral stenosis there may be laid down in the lung tissue iron deposits from the infiltration of blood and these deposits may give rise to a characteristic x ray picture of miliary pulmonary hemosiderosis The liver becomes congested only when the right heart fails but such congestion over the years may lead to a moderate cardiac cirrhosis of the liver

Symptoms There are no symptoms of mitral valve disease except for evidence of the limited air space in the lungs in most cases Dyspnea on effort is common when the mitral valve disease is more than slight in degree while indication of a high degree of pulmonary engorgement from marked mitral stenosis is dyspnea even at rest or in paroxysmal attacks (with or without acute pulmonary edema or cardiac asthma) when the heart rate suddenly increases The dyspnea in mitral stenosis is not to be attributed to failure of the myocardium it is due to the mechanical effect of the stenosed mitral valve Cough and hoarseness due to the pressure from a very large left atrium are uncommon symptoms as is also hemoptysis due to pulmonary apoplexy

Vieussens R *Traite Nouveau de la Structure et des Causes du Mouvement Naturel du Coeur* Jean Guillemette Toulouse 1715 pp 105 and 106 (Translation by myself)

I perceived that the opening into the left ventricle appeared very small and was of an oblong oval shape and in seeking the cause of such a surprising fact I discovered that the cusps of the mitral valve were truly bony and so thickened and contracted that they very much narrowed the ostium

The entrance into the left ventricle having been much narrowed and its margin having lost all its natural suppleness the blood could no longer enter so freely and abundantly as would be necessary into the cavity of this ventricle in consequence of the embarrassment of the circulation the blood began to dilate extraordinarily the trunk of the pulmonary vein [that is the left atrium] because it remained there so long and collected in such a great quantity The blood had no sooner begun to make too long a stay in the main trunk of this vein than it delayed the course of blood in all the blood vessels of the lung so that the branches of the pulmonary artery and vein extending throughout all the tissues of the lung were always too much filled with blood and consequently so dilated that they compressed the vesicles to such an extent as to hinder the air from entering and leaving freely *that is why the patient breathed always with much difficulty* (Italics mine)

Complications like congestive heart failure atrial fibrillation pulmonary embolism massive left atrial enlargement, and acute rheumatic or bacterial endocarditis may produce symptoms which are discussed in the chapters in this book dealing with these subjects Angina pectoris in mitral stenosis is rare having been found in only 2 6 per cent of Levine and Kauver s 741 cases (1942) and then almost always due to an incidental complication of coronary heart disease there were however three of these authors cases of mitral stenosis with angina pectoris who showed no significant coronary artery disease and these plus a few others seen by ourselves and by other observers (Blackford 1940 Dressler 1942) indicate the probability that in rare cases

of marked mitral stenosis the output of blood from the heart may be inadequate to meet the needs of the coronary circulation on effort

Signs There are only two pathognomonic signs of mitral valve disease one auscultatory and the other roentgenologic Both show the presence of mitral stenosis Mitral regurgitation due to valvular disease cannot be easily differentiated from mitral regurgitation due to ventricular dilatation except *when it is combined with proof of mitral stenosis*

The auscultatory proof of mitral stenosis is the presence of a rumbling apical middiastolic murmur (Figure 15, page 95) with or without presystolic accentuation in the absence of considerable aortic regurgitation or other cause of left ventricular dilatation It was first recognized by C J B Williams more than a century ago but his description went unheeded until the present generation again called attention to it as an essentially diastolic and not merely a presystolic murmur

Williams C J B *Diseases of the Chest* John Churchill Publisher London 3d edition 1835 p 198

Mitral valve Obstructive disease of this valve commonly consists in an adhesion together or ossification or rigidity of some of its parts or in a thickening and contraction of the fibrous ring at its base It may cause a murmur with the diastole of the ventricle and therefore at the time of the 2nd sound for although th ventricle in itself produces no sound yet when the orifice by which it becomes refilled is contracted the current being partially resisted in passing through may become sonorous This will therefore leave the result much as Laennec represented it inasmuch as there is a current from the auricles to the ventricles during the diastole of the latter although *this current is not produced* as he supposed, by the contraction of the auricles But the results of my late experiments must mod fy the statements of both M Laennec and Dr Hope in this respect that the con traction of the mitral orifice with its impeded current and attendant murmur will not necessarily supplant the 2nd sound inasmuch as this sound is seated in the semilunar valves the action of which may still be perfect

The roentgenologic proof of mitral stenosis is the presence of a considerabl increase in the size of the shadows of the right ventricle and of the pulmonary artery combined with well marked enlargement of the left atrial shadow, or the latter finding with any type of ventricular enlargement left right or combined (Figure 127) Given either or both of these auscultatory and roentgenologic findings and they are usually combined the presence of a apical systolic murmur means mitral regurgitation as well as mitral stenosis and is due to the valvular disease (provided a respiratory murmur can be excluded) A large left atrium raises the left bronchus

Other signs strongly suggesting though not proving mitral disease include a loud apical systolic murmur without any diastolic murmur in the absence of any acute or subacute illness or of evidence of left ventricular enlargement Appreciable left ventricular enlargement would of course indicate that the cause of such a murmur could well be ventricular dilatation The history of

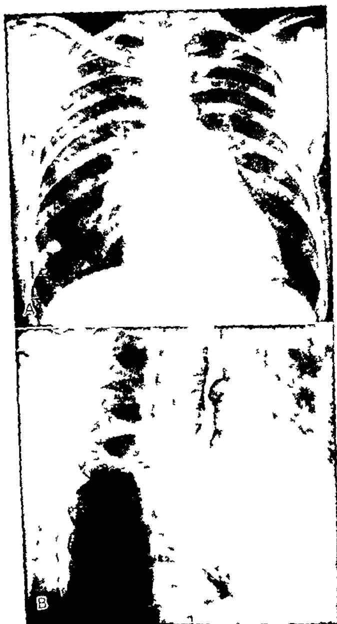


FIG 1 7 Roentgenograms showing a heart with a high degree of mitral stenosis a big right ventricle and marked enlargement of the left atrium which bulges to the right above the right atrium in the anteroposterior view (*A*) and posteriorly into the shadow of the spine in the right anterior oblique view (*B*) *Note the displacement* of the barium filled esophagus by the broad curve of the left atrium below the aortic and pulmonary artery notches in the oblique view

rheumatic infection in the past makes this apical systolic murmur all the more important evidence of mitral disease

Another corroborative sign of mitral disease is accentuation of the first heart sound at the apex which as Cossio has shown (1943) may be delayed in relation to the onset of systole (due to the hemodynamic conditions present) and preceded by a short period of systolic vibration which may or may not be in turn preceded by a true presystolic murmur Less important corroborative signs are accentuation of the second sound at the pulmonary area the presence of atrial fibrillation under the age of forty years increased prominence of the left upper border of percussion dullness or roentgen ray shadow and increased width and depth of the lung hilus shadows by roentgen ray (due to the dilatation of the pulmonary blood vessels)

A diastolic thrill limited to the apex merely accompanies a marked mitral diastolic murmur

Another strongly suggestive and practically pathognomonic sign of mitral disease is the electrocardiographic evidence of abnormal right ventricular preponderance combined with atrial fibrillation The abnormal right ventricular preponderance alone with normal rhythm and increased atrial or P waves is found also in congenital pulmonary stenosis or interatrial septal defect but with a rheumatic history and a systolic murmur limited to the apex it strongly favors mitral valve disease the occurrence of atrial fibrillation with abnormal right ventricular preponderance is rare in congenital heart disease and common in mitral disease (Figures 128 and 129)

The blood pressure is of no importance in the diagnosis of mitral disease it may be normal low or high A low systolic pressure with small pulse pressure is common but hypertension of the essential type is a not infrequent complication even in well marked mitral stenosis

Other signs found with mitral disease are merely those due to various complications

Course and prognosis The chief cause of chronic crippling of the heart in young adults is extensive mitral disease of rheumatic type lesser grades of mitral stenosis or regurgitation or of both combined often permit long lives with relatively little crippling

The course and prognosis of mitral disease vary according to the extent of the lesion the etiologic factors, and the complications The lesion may be so slight that there is little or no deformity of the valve with little or no stenosis or regurgitation in such cases the course is that of a person with a normal heart and the prognosis is excellent with but one exception which is however important A damaged mitral valve whether or not discovered clinically is a liability in that it is much more frequently than is a normal valve the site of repeated rheumatic infection in youth and if there is not much mitral stenosis of bacterial endocarditis in youth and middle age

If there is marked and preponderant stenosis of the mitral valve in youth the victim develops symptoms and signs of diminished cardiac reserve and frequently of atrial fibrillation (in over one half of the cases) and dies usually

of congestive failure due to right ventricular exhaustion in young adult life or middle age especially in the presence of a recurrent rheumatic infection or pulmonary infarction The high pressure in the pulmonary circulation occasionally results in bleeding slight as shown by bloodstained sputum or extensive with hemoptysis Occasionally complications like pericarditis or cerebral embolism from intra atrial thrombosis in the cases with atrial fibrillation hasten death The duration of life after the establishment of well marked mitral stenosis averages ten to twenty years but occasional cases far exceed this length of time while other cases die within a few months to a year or

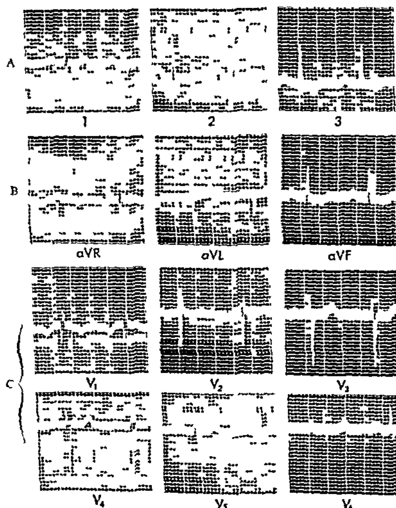


FIG 128 Electrocardiogram in a case of *mitral stenosis* showing normal rhythm, female age 45 (*A*) Bipolar limb leads 1 2 and 3 (*B*) unipolar limb leads aVR aVL, and aVF (*C*) six precordial leads V_1 to V_6 inclusive Note right axis deviation in limb leads and wide *P* waves Time = 0 04 and 0 20 second amplitude 1 mm = 0 10 mv

two In the last edition of this book I noted that four cases of moderate degrees of rheumatic mitral stenosis exceeding the age of 80 years and proved at autopsy had come to my notice (White and Bland 1941) in one of the four namely Dr Herman F Vickery there had never been any cardiac symptoms during a very active life until angina pectoris on effort due largely or wholly to coronary heart disease developed at the age of 77 years At autopsy after death from pneumonia in his eighty fourth year the heart was

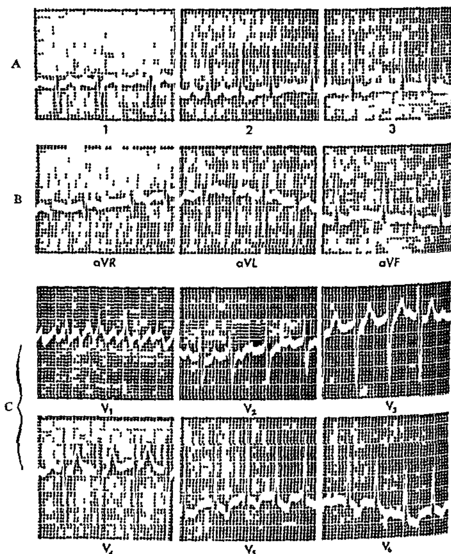


FIG 129 Electrocardiogram in a case of mitral stenosis showing coarse atrial fibrillation and right axis deviation female age 14 (*A*) Bipolar limb leads 1 2 and 3 (*B*) unipolar limb leads aVR aVL and aVF (*C*) six precordial leads V to V inclusive Note also the regular rapid atrial action (450 per minute) resembling flutter in Lead V Time = 0 04 and 0.20 second amplitude 1 mm = 0 10 mv

but slightly heavier than normal and the left atrium was very little if at all enlarged (the heart rhythm had been normal) Since 1941 I have encountered several more very old persons with rheumatic mitral stenosis

Marked mitral regurgitation is a greater strain on the heart than is mitral stenosis and life is shorter usually lasting but a few years at best It should be emphasized again that the degree of mitral regurgitation is indicated roughly by the intensity of the apical systolic murmur in that the murmur is loudest, other things being equal when the regurgitation is moderate and faintest when the regurgitation is only very slight or else of extreme degree as discussed in Chapter 5 If the mitral ostium remains wide open during systole there should be no mitral systolic murmur at all such a possibility is however remote

Complications The commonest complications of mitral disease have already been mentioned (1) pulmonary congestion without heart failure (2) right ventricular failure (3) atrial fibrillation and (4) pulmonary embolism with infarction. Pulmonary congestion is especially common and slight bleeding from this or very rarely brisk hemoptysis from rupture of a larger pulmonary blood vessel (pulmonary apoplexy) may occur Sudden flooding of the pulmonary circulation in mitral stenosis by overactivity of the strong right ventricle due to tachycardia from effort or excitement or paroxysmally occasionally precipitates a paroxysm of dyspnea which may or may not be asthmatic (one type of cardiac asthma—McGinn and White 1934)

However *it is very important not to confuse this picture of pulmonary congestion with that of pulmonary embolism with infarction which is also a common complication of mitral stenosis and one often disregarded or overlooked* (Levine and White 1937) an unrecognized venous thrombosis especially in the leg of a patient with mitral stenosis and congestive failure is more often responsible for such pulmonary embolism than is an intracardiac thrombus in the right heart chambers and is of course more amenable to treatment (by ligation) The thrombosis may be concealed in a leg already swollen in congestive heart failure and the pulmonary infarction may be concealed by congestive rales or hydrothorax in such a case but unexplained fever leukocytosis tachycardia and sometimes hemoptysis and jaundice are clues calling attention to this complication

Congestion of the liver due to stasis in the right heart chambers and inferior vena cava with particular effect on the low pressure in the hepatic veins is frequent. After years of such hepatic congestion liver atrophy is found along with areas of regeneration and finally a real cirrhosis may develop with ascites out of proportion to the degree of dependent edema Intra atrial thrombosis rarely of the ball type loose in the atrium sometimes occurs in mitral disease (more often in the cases showing atrial fibrillation) pieces of such thrombi may be thrown off to brain kidneys spleen or extremities as aseptic emboli A ball thrombus may rarely block the circulation completely but transiently with evidence of such obstruction in the peripheral circulation (absent pulses cadaveric discoloration of fingers and toes) and brain. Marked

enlargement of the heart chambers especially of the left atrium may cause pressure symptoms and signs in the thorax such as cough and very rarely recurrent laryngeal nerve paralysis (produced probably by pressure from the pulmonary artery pushed up against the aortic arch by the enlarged left atrium) Recurrent rheumatic infection is common in the younger cases and subacute bacterial endocarditis is an occasional fatal complication Apparently valvular stenosis protects somewhat against Streptococcus viridans endocarditis probably through failure of the valve to clo e in systole there no longer being the factor of trauma at the valve line of closure to favor th lodgment of the bacteria Angina pectoris rarely complicates mitral stenosis (see comment under Symptoms)

Rupture of the mitral valve may occur when inflamed or from trauma and rupture of the chordae tendineae which may lead to serious mitral regurgita tion and congestive heart failure (Bailey and Hickam 1944)

Other types of heart disease thyroid hypertensive and coronary are at times associated with mitral valve disease syphilitic aortitis is rarely a complication Other valve lesions are often found with mitral valve disease especially those of the aortic valve A variable degree of tricuspid valve disease is found in about one quarter of all cases of mitral valve involvement percentages of 15 up to 40 have been reported An interesting complication of mitral stenosis is congenital deficiency of the atrial septum discussed in Chapter 13 th septal defect diverts blood into the right atrium probably almost doubling the load on the pulmonary circulation and resulting in much greater enlargement of the right heart chambers than of left

Neurocirculatory asthenia and cardiac neurosis frequently complicat mitral disease the latter particularly as the result of exaggeration of the im portance of heart murmurs by the physician Various other illnesses and in fections and diseases of other organs may occur but tuberculosis of the lungs is infrequently found in the presence of marked mitral stenosis

Treatment In the last edition of this book (1944) I stated that there was no specific therapy for mitral valve disease that complications must be treated as such and that the life of a person with mitral disease should be somewhat protected especially against heart failure and against infection of rheumatic and subacute bacterial nature but during the last few years progress has been made in two directions both surgical An ingenious and successful anastomosis between one of the right pulmonary veins and the vena azygos has been carried out in several cases of tight mitral stenosis to prevent recurrent attacks of severe acute pulmonary edema through the establishment of a safety valve (Bland and Sweet 1949) an atrial septal defect has been produced for the same purpose (Harken Ellis et al 1948) The oth r procedure has been the evolution of more promising plastic surgery on the deformed valve itself (Bailey et al 1949 Harken 1950 and others) than the pioneer efforts of Cutler which had to be abandoned because of a very high mortality over twenty years ago (Cutler and Beck 1929) The best technic now (early in 1951) is the incision or rupture of the cusp adhesions at the

commissures The next decade may be a crucial one of further progress in valvular surgery but of far greater importance of course will be efforts also beginning to look promising to control the chief cause of valvular deformity namely rheumatic fever itself

Differential diagnosis Mitral valve disease must be primarily differentiated from functional mitral regurgitation from respiratory systolic murmurs from relative mitral stenosis in cases of left ventricular dilatation with or without aortic regurgitation from transmitted murmurs of aortic stenosis of tricuspid stenosis and of congenital defects (pulmonary stenosis and interventricular septal defects) and from the overactive heart in thyrotoxicosis or neurocirculatory asthenia The signs whereby this differentiation may be made have already been discussed here I would simply reiterate that with considerable cardiac enlargement it is sometimes impossible to distinguish by clinical examination mitral valvular disease from the manifestations of left ventricular dilatation Finally it should be said that occasionally mitral disease even of extensive degree may exist without proof of its existence especially when the heart action is weak the heart very large or some overshadowing complication present

B AORTIC VALVE DISEASE

Aortic valve disease is generally considered to be more serious than mitral valve disease The chief reason for this is that aortic valve disease is often caused by a neglected syphilitic infection Moreover slight degrees of involvement are frequently missed in diagnosis the soft aortic diastolic murmur being unheard and the systolic murmur of slight aortic stenosis unattended by a thrill being disregarded because of the absence of all other signs As a matter of fact disease of the aortic valve is often of very slight degree and when it results from a rheumatic infection in youth it may be compatible with a long and fully active life

Etiology *Cause* The cause of aortic valve disease is commonly either rheumatic or syphilitic the former occurring more often in such parts of the world as New England where the rheumatic infection is common and the latter more often in regions where syphilis is more frequent and rheumatism relatively infrequent Other causes of aortic valve disease are relatively rare and consist of bacterial endocarditis collagen diseases and sclerosis The valve ring itself may be stretched with or without any lesion of the valve cusps this fact explains the aortic regurgitation in certain cases of syphilitic aortitis or of chronic hypertension especially when aortitis and hypertension are combined and in rare cases of severe anemia in a series of 200 consecutive autopsied cases of hypertensive heart disease with normal aortic valves an aortic diastolic murmur had been found in 14 i e 7 per cent (Garvin 1940) Trauma is a very uncommon cause of aortic valve lesions it occurs particularly in the case of a valve already damaged Congenital aortic valve defects are infrequently found the bicuspid valve is the commonest

Age The age at which aortic valve disease is present extends from early childhood to extreme old age It is commonest in middle age when the rheumatic aortic valve lesion is still encountered the syphilitic lesion most frequent and the sclerotic type beginning to appear

Sex The male sex shows much more aortic valve disease than does the female sex in about the ratio of 3 to 1 This is due not only to the fact that syphilitic aortitis is much more common in the male but also to the fact that the rheumatic infection involves the aortic valve more often in the male and that sclerotic changes are also more common in that sex

Pathology The pathology of aortic valve disease depends on the etiologic factor Active inflammation of the valve has already been discussed at the beginning of this chapter and in Chapters 14 15 and 16 It remains to discuss the chronic deformities of the valve and their effect on the heart and aorta

(a) A single mild *rheumatic* valvulitis may leave no deformity, but severe or repeated infections tend to cripple the valve through adhesion of the cusps at their commissures thereby producing stenosis of various degrees or through scarring retraction and stiffening of the free borders of the cusps thereby producing regurgitation As in the case of the mitral valve so here too the rheumatic lesion usually causes both stenosis and regurgitation giving rise rarely to regurgitation alone except in the earliest stages and also rarely to stenosis alone There are varying ratios of stenosis and of regurgitation in different cases and during the evolution of a single case The end result of a rheumatic lesion or of repeated rheumatic lesions may be either preponderant aortic stenosis (Figure 130) preponderant aortic regurgitation or equal grades of both from the clinical standpoint it is useful to attempt to make this differentiation Preponderant regurgitation is much more common than preponderant stenosis in the ratio of about 5 to 1, but in New England pure aortic regurgitation as determined at postmortem examination is less common than the combination of aortic stenosis and regurgitation In Cabot s series (1926) there were 93 cases showing stenosis and regurgitation of the aortic valve and 55 cases showing regurgitation with little or no stenosis which gives a proportion of 148 instances of aortic regurgitation to 93 of aortic stenosis The healed rheumatic aortic valve may become calcified and stony especially when there is marked stenosis

(b) In *subacute and acute bacterial endocarditis* the vegetations may be so large that they cause actual stenosis, or increase it if stenosis is already present, they may even project upward from the cusps and block the mouths of the coronary arteries There may be extensive ulceration of the valve cusps with rupture or the development of small aneurysms of the sinuses of Valsalva Usually bacterial endocarditis is superimposed on an aortic valve previously damaged by rheumatic infection or on a congenitally abnormal valve (bicuspid especially) but it may attack a normal valve and in the early stages as in the case of the rheumatic lesion there may be no deformity Permanent deformity may result consisting of stenosis regurgitation or both with a tendency to calcification of the damaged valve

(c) As the result of *syphilitic* involvement the commissures of the aortic valve become permanently widened to cause regurgitation (Figure 131) The aortic valve ring also may be dilated with the development of extensive regurgitation Aortic stenosis is not the result of syphilis itself although rarely in healed cases complicating calcification or subacute bacterial endocarditis may cause some degree of stenosis

(d) The *sclerotic* lesion of the aortic valve found as a primary condition in older individuals (Monckeberg 1904) is not commonly of a degree sufficient to cause much deformity of the valve It is a different process from that of secondary calcification of rheumatic or other types of infectious endocarditis although they may exist together The sclerotic lesion is a subendocardial process beginning as atheroma and progressing to calcification especially at the base of the valve as it increases it grows into the valve cusps stiffening and deforming them first at their bases and producing a slight aortic stenosis This kind of aortic stenosis probably accounts for an aortic systolic murmur in some elderly individuals in whom there is no evidence of aortic dilatation a diagnosis of aortic dilatation has at times been made unjustifiably to explain an aortic systolic murmur of obscure origin When the whole valve is involved and a stony mass projects into the aortic lumen

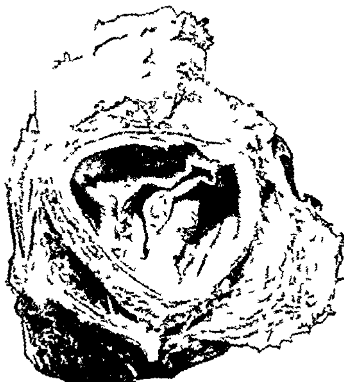


FIG 130 Photograph showing marked aortic stenosis Bicuspid valve (Kindness of Dr Ronald Grant Guy's Hospital London)

resulting in well marked aortic stenosis Monckeberg s sclerosis alone usually is not to blame but rather a combination of an old infectious process and superimposed calcification In a series of 40 cases of calcific sclerosis of the aortic valve studied microscopically with care only 3 cases were thought to fit pure Monckeberg s sclerosis of the remaining 37 18 were clearly rheumatic in origin and another 19 probably so (Karsner and Koletski 1940) The endocardium may be eroded just as the endothelium in the aorta is at times eroded over calcified plaques

(e) Serious *congenital* aortic valve lesions stenosis and atresia are very rare but congenital bicuspid aortic valves are found occasionally and are likely to be the site of subacute bacterial endocarditis quadricuspid aortic



FIG 131 Syphilitic aortitis and aortic insufficiency The aortic valves are thickened and rolled at their margins and widely separated at the commissures The coronary mouths are obliterated Note wrinkling and stellate scarring of aortic intima The left ventricle is dilated and the trabeculae carneae flattened—evidence of aortic regurgitation (W G MacCallum *A Text Book of Pathology* 1928 Kindness of W B Saunders Company Philadelphia)

valves are seldom encountered Subaortic stenosis involving the infundibulum (outflow tract) of the left ventricle is more often found as a congenital defect than stenosis of the valve itself but both are rare

(f) *Rupture* Blows and very rarely indirect strain may cause linear ruptures of the aortic cusps at their bases or through their structure anywhere even when no disease is present probably due to a high pressure effect at the moment of valve closure associated with inferiority of tissue strength Almost invariably however lesions due to acute or subacute bacterial endocarditis or to syphilis are the cause of weakening of the valve before rupture takes place When there is some such disease present no definite trauma is needed to cause rupture, ordinary cardiac action being sufficient

Normally in the adult the aortic valve ring circumference measures 7 to 8 cm if it measures 5 cm or less the stenosis is marked enough to be of considerable clinical importance and should be clinically diagnosable

Effect of aortic valve disease on the heart The effect of aortic valve disease on the heart itself is very variable There may be no evident effect when there is no valve deformity or when there is very slight regurgitation or stenosis Marked *aortic regurgitation* has a more rapidly serious effect than has marked aortic stenosis The heart becomes very large with the apparently simultaneous development of left ventricular hypertrophy and compensatory dilatation producing eventually the cor bovinum the ox heart which may weigh as much as 1 000 gm or more and which is as a rule widely dilated The heart of pure aortic regurgitation is on the average the heaviest and largest known It is most often seen in syphilitic aortitis but occasionally it results from the rheumatic infection When the left ventricular dilatation in aortic regurgitation reaches a certain degree the mitral valve no longer remains competent and left atrial enlargement (dilatation and hypertrophy) ensues followed in turn by right ventricular enlargement and eventually by right atrial enlargement too though death due to left ventricular failure is likely to interrupt the full evolution of these various steps Pulmonary congestion occurs after the left ventricle has begun to fail

The heart muscle may be unaffected in cases of marked aortic regurgitation other than to show great hypertrophy and to be stretched around a widely dilated left ventricular cavity with flattened trabeculae This strong and seemingly healthy muscle may fail under the strain of the overwork which is caused by the valve lesion abetted by defective coronary circulation which in turn is the result of the low diastolic blood pressure Normally it is a sufficient blood pressure in diastole that maintains the coronary circulation at a proper level Although narrowing of the coronary artery mouths by the aortitis so often accompanying aortic regurgitation may still further weaken the myocardium actual pathologic changes in the myocardium are only infrequently seen when such changes do occur they result from concurrent occlusion or much sclerotic narrowing of the coronary arteries or from rheumatic myocarditis if there is an active rheumatic infection

Marked *aortic stenosis* generally of gradual development causes steadily

increasing hypertrophy of the left ventricle with little or no dilatation until the heart begins to fail The hypertrophy is of the concentric type as compared with the eccentric type in aortic regurgitation and the heart remains relatively small in bulk although considerably increased in weight Eventually the heart in aortic stenosis may become two or three times the normal weight but this occurs much more readily if considerable aortic regurgitation is also present The other heart chambers are unaffected in aortic stenosis until the left ventricle fails It is surprising to discover how well aortic stenosis may be borne even by old persons and yet it must be considered a constant strain on the left ventricle and a possible cause of sudden death Congenital subaortic stenosis acts on the heart much as does acquired aortic stenosis itself

Effect of aortic valve disease on the aorta Aortic dilatation is commonly found with marked aortic regurgitation especially when the aorta is the seat of a syphilitic process with loss of its elasticity and muscular continuity even with rheumatic aortic regurgitation the aorta becomes somewhat stretched, but not so much permanently as temporarily with each systole In cases of preponderant aortic stenosis the aorta may be normal in caliber and in other respects also

Symptoms The only symptoms of aortic valve disease itself are a tendency to faintness dizziness or even syncope in patients with marked aortic stenosis and to throbbing forceful pulsation of heart and arteries in patients with marked aortic regurgitation. In advanced cases it is common to find symptoms of left ventricular failure such as paroxysmal dyspnea with or without cardiac asthma and of coronary insufficiency (angina pectoris) without other cause than the aortic valve disease in some young individuals usually of nervous type, aortic regurgitation especially when marked in degree is attended by paroxysmal angina pectoris and hypertension even at rest

Signs The early stage of acute rheumatic aortic valve involvement and even the chronic aortic valve lesion too may be so slight in degree that there is no valve deformity and therefore no sign of disease of the valve The same is true of acute bacterial endocarditis of syphilitic invasion and of sclerotic change in their earliest stages but when the valve is deformed there are always signs of its affection except in moribund conditions The clinical proof of aortic valve disease rests primarily on auscultatory findings

Aortic stenosis when very slight is without signs or attended by only a minimal systolic murmur when of moderate degree it is accompanied by a loud systolic murmur in the second intercostal space just to the right of the sternum with or without a slight palpable thrill and with slight to moderate cardiac enlargement of the left ventricular type When the stenosis is of considerable degree the aortic systolic murmur is very harsh and widely transmitted especially along the great vessels toward neck and arms and even into the abdominal aorta the aortic systolic thrill is marked the second aortic sound is often absent the heart is considerably enlarged and the peripheral pulse is small and often of plateau or anacrotic type with low systolic and small pulse pressure (see Chapter 8)

The triad of murmur thrill and small pulse is the essential finding the other findings are corroborative It is not necessary however to wait for an aortic systolic thrill or a plateau pulse to make a diagnosis of aortic stenosis the diagnosis can be made on the aortic systolic murmur alone in a patient without aortic dilatation or hypertension provided the murmur is loud and harsh Accuracy of diagnosis has increased greatly in our hands since we have made this change in the diagnostic criteria of aortic stenosis It is furthermore of great interest to remember that the systolic murmur of aortic stenosis is well transmitted to the cardiac apex but not to the lung bases in back while the systolic murmur of mitral regurgitation is well transmitted to the lung bases in back but not to the base of the heart The heart rhythm is usually normal in aortic stenosis

There is a characteristic roentgen ray picture of the heart somewhat enlarged by the presence of relatively uncomplicated aortic stenosis (without hypertension or myocardial failure and with little or no aortic regurgitation) there is a compact concentric enlargement of the left ventricle without increase of pulmonary artery and with little aortic prominence (Figure 132) The electrocardiogram in time develops the pattern of left ventricular enlargement (high *R* waves and depressed or inverted *T* waves in Lead 1 and in the precordial leads over the left ventricle V_4 V_5 and V_6) (Figure 133 page 691) as in the case of the hypertensive heart (see Figure 97, page 477)

The signs of congenital subaortic stenosis are essentially the same as those of acquired aortic stenosis

Aortic regurgitation is shown by the presence of an early blowing diastolic murmur heard maximally along the left sternal border over the sternum itself at the level of the second and third ribs or in the second intercostal space just to the right of the sternum provided one can rule out pulmonary regurgitation which is a very rare valve defect Pulmonary regurgitation can almost invariably be excluded by the absence of marked mitral stenosis (which is the usual factor behind pulmonary regurgitation) and by the absence of the very rare congenital or acquired pulmonary valve disease with regurgitation

The heart may not be found appreciably enlarged on either physical or roentgenologic examination in the presence of a slight degree of aortic regurgitation which is sufficient nevertheless to give a characteristic murmur nor need there be in such cases any abnormality of blood pressure or of the character of the peripheral pulse Cardiac enlargement particularly of left ventricular type is readily found by any method of study in the presence of considerable aortic regurgitation associated with such enlargement are a full pulse pressure due to a low diastolic pressure (often as low as 30 or 40 mm of mercury and sometimes not measurable above zero) a water hammer pulse capillary pulse in very rare cases even pulsation of the spleen a double murmur in the great arteries when compressed (Duroziez s sign Duroziez 1861) and a double murmur at the base of the heart The roentgen ray in such cases besides showing the left ventricular enlargement (Figure 132)

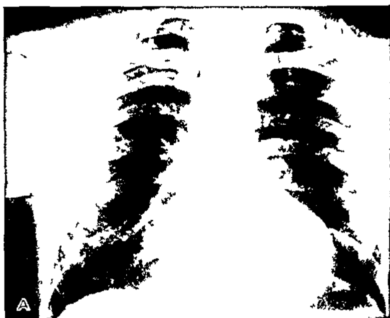




FIG 132 Roentgenograms of the thorax in two cases of aortic valve disease (*A*) stenosis (*B*) regurgitation Both young men (Kindness of Dr Hugo Roesler Temple University Philadelphia)



FIG 133 Electrocardiogram in a case of aortic stenosis with enlargement of the left ventricle f male age 59 (*A*) Bipolar limb leads 1 2 and 3 (*B*) unipolar limb leads aVR aVL and aVF (*C*) six precordial leads V to V inclusive Note especially *the deep S waves in Leads V to V inclusive* and the high *R* waves and inverted *T* waves in Leads 1 2 V and V_6. Time = 0 04 and 0 20 second amplitude 1 mm = 0 10 mv

usually reveals a full ventricular pulse with increased pulsation in the aorta The electrocardiogram usually shows abnormal left ventricular preponderance with high *R* waves and inversion of the *T* waves in Leads 1, V_4 V_5 and V_6 in these marked cases very similar to the record in marked aortic stenosis (see Figure 133 page 691) If we wait however for all the confirmatory signs of marked aortic regurgitation before making the diagnosis we shall miss about half of the cases namely, those in which the lesion is too slight to give more than the characteristic murmur and perhaps a little cardiac enlargement.

A combination of aortic stenosis and aortic regurgitation gives signs mid way between the extreme signs of the individual defects

Course and prognosis Slight grades of aortic valve disease of rheumatic origin appearing in youth and sometimes discovered accidentally on routine examination are often well supported without symptoms during long and active lives Such lesions are however always a menace because of the possibility of recurrent rheumatic infection with more definite crippling or of bacterial endocarditis superimposed on the valve already damaged Marked aortic regurgitation is always a serious burden and if it is of syphilitic origin it may not permit more than a few years of life Although marked aortic stenosis is also an important burden it is a lighter one than marked aortic regurgitation in part because an active syphilitic process is not a factor in some cases it may limit the duration and activity of life relatively little and I have found the gradual development of aortic stenosis over a period of years a good omen in a young adult who starts off with a considerable degree of rheumatic aortic regurgitation However in either case regurgitation or stenosis the less the physical strain or frequency of infection the longer the life Congestive heart failure and angina pectoris are frequent causes of death in aortic valve disease Also unexplained syncope and sudden death are not rare in aortic stenosis of high degree Sudden death in aortic stenosis was first recorded by Bonetus in 1679 (see below) it occurred in 18 per cent of 100 cases of calcareous aortic stenosis analyzed by Horan and Barnes (1948) When congestive failure first appears in either aortic stenosis or aortic regurgitation it is difficult to control recurs quickly and indicates usually a short survival of a few months to a year or two

Bonet T *Sepulchretum sive Anatomia Practica* Leonard Chouet Geneva 1679 Vol I Book II Section XI (De morte repentina on sudden death) Observation XXVI (Translation my own)

Anatomy of a man who died suddenly and whose semilunar valves situated at the mouth of the aorta were turned to bone

A Parisian tailor residing in the district of St James full blooded and inclined to obesity and not yet old having dined and left his house had walked hardly 40 paces when he suddenly fell to the ground and expired

Carried back to his home his body was opened and no disease was found anywhere except that the three semilunar cusps situated at the entrance of the aorta from the left ventricle were discovered to be bony I received one of these as a

gift and found it of whitish color and so hard that it could hardly be incised with a knife

Complications Aside from the complications of mitral valve disease congestive failure angina pectoris and subacute bacterial endocarditis in aortic valve disease other direct associations are rare For instance atrial fibrillation is infrequent and hypertension is not very common Coronary disease of high degree is however sometimes found as is also neurocirculatory asthenia and it is important to note that the blood pressure may be quite high even in the presence of marked aortic stenosis

Treatment There is as yet (1950) no adequate reparative treatment for aortic valve disease itself although much promising research is in progress with respect both to plastic surgery and to artificial valves * however the etiologic factors—syphilis and rheumatism—should be treated if they are still active Congestive failure and angina pectoris should receive therapy as such without regard to the valvular disease

The discovery of aortic valve disease even of slight extent demands some consideration it should neither be exaggerated nor underrated The individual should not be made into a neurotic cripple on the other hand he should be given an intelligent explanation of his trouble and advised to protect himself against strenuous exertion or fatigue Foci of infection should be eradicated and respiratory infections should particularly be avoided Penicillin should be administered at the time of dental extractions to give protection against subacute bacterial endocarditis

Differential diagnosis Aortic valve disease must be differentiated from functional aortic regurgitation pulmonary regurgitation pulmonary stenosis patent ductus arteriosus interventricular septal defect aortic dilatation or aneurysm a venous hum in the neck transmitted to upper chest and marked peripheral vasodilatation The differentiation is generally easy the commonest errors are in confusing dilatation of the aorta with aortic stenosis and in overlooking slight aortic regurgitation The discussion above of the signs in aortic valve disease covers the differential points It may be impossible to distinguish aortic regurgitation due to valvular disease from that of functional type the latter is so much less common however that it is generally safest to disregard the possibility of its occurrence in an individual case except in severe anemia or in a case of chronic hypertension with variable aortic diastolic murmur As a rule when functional aortic regurgitation is diagnosed clinically it is found at postmortem examination that aortic valve disease is present The greatest problem of all lies in the differential diagnosis of etiologic factors behind aortic regurgitation sometimes this problem is insoluble during life despite careful study and even postmortem examination may fail to give the answer

C TRICUSPID VALVE DISEASE

Tricuspid valve disease has been of very little clinical importance as compared with disease of the mitral aortic and even of the pulmonary valves

* Most recently (autumn 1951) surgical approach to the problem by dilatation of the stenosed aortic valve is being explored by Bailey of Philadelphia.

The reasons for this are three In the first place deformity of the valve sufficient to be of clinical significance is rare Secondly, when such deformity is present it is usually overshadowed by a higher and much more important degree of mitral valve disease And thirdly except in rare instances tricuspid valve disease has not been diagnosed ante mortem though it has been sometimes suspected Recently however there has been an improvement in the accuracy of diagnosis as witness a 34 per cent correct diagnosis in fifty cases of tricuspid stenosis found among 150 patients with rheumatic heart disease studied post mortem (Aceves and Carral 1947)

Tricuspid valve disease rarely occurs without other valve lesions In a series of 173 cases (Osler and Gibson 1915 including for the most part cases originally collected by Leudet 1888) tricuspid stenosis is said to have been found alone in only 12 and in all these 12 the lesion was apparently of congenital origin in 158 there was also a mitral lesion further complicated by an aortic valve lesion in 58 and by a pulmonary valve lesion in 3 in 3 cases the tricuspid and pulmonary valves were involved None of the 30 cases of tricuspid stenosis personally observed by Dressler and Fischer (1929) were uncomplicated by mitral valve disease In another study 39 per cent of cases with both mitral and aortic valve disease had also tricuspid stenosis of some degree (Einsel Feil and Stone 1931) A later analysis by Cooke and White (1941) has shown affection of the tricuspid valve in 47 (22 per cent) of 217 cases of rheumatic heart disease among 4 300 autopsies at the Massachusetts General Hospital between 1920 and 1937 but in only 30 of these (14 per cent) was tricuspid stenosis thought to be of sufficient degree to be of clinical importance Another study by Smith and Levine (1942) revealed 32 cases of tricuspid stenosis among 340 individuals with rheumatic valvular disease in 4 437 autopsies at the Peter Bent Brigham Hospital from 1913 to 1940 inclusive

Etiology The causes of tricuspid valve disease are exactly those of mitral disease most commonly the rheumatic type of infection with verrucose endocarditis thickening of the valve on healing with fusion of cusps and fusion and shortening of the chordae tendineae in advanced cases Acute and subacute bacterial endocarditis sclerosis and trauma are rare causes of tricuspid disease as are also such congenital defects as displacement and insufficiency (Ebstein 1866 Yater and Shapiro 1937) stenosis and atresia

The *age* and *sex* incidences of tricuspid valve disease correspond roughly to those of mitral disease children and young adults chiefly being affected and females slightly more often than males although in one series of cases the sexes were evenly divided (21 to 21) and the age at death averaged very much less than that in rheumatic heart disease in general (23 years as compared with 42 years) (Cooke and White 1941)

Pathology Pathologically in tricuspid valve disease as in the case of the mitral valve regurgitation and stenosis are almost invariably associated although either one may preponderate Stenosis of clinical importance and in some cases diagnosable clinically is reached when the circumference of the adult tricuspid valve ostium normally 11 to 13 cm (average 12 cm) is reduced

to 8 cm or less The appearance of the stenosed tricuspid valve is much like that of the stenosed mitral valve in fact when there is a tricuspid diaphragm with a small ostium in its center a view from above looking into both atria gives a strikingly symmetrical appearance on both sides Functional tricuspid regurgitation is common with right ventricular dilatation associated with congestive heart failure (Figure 126 page 671) but occurs also with other factors like anemia and pulmonary regurgitation

Effect of tricuspid valve disease on the heart Well marked tricuspid stenosis if uncomplicated naturally affects little of the heart itself except the right atrium which becomes enlarged tricuspid regurgitation causes enlargement of both right heart chambers Since however there is practically always involvement of some other valve as well as of the tricuspid one finds a combination of effects on the heart chambers Practically speaking tricuspid stenosis acts wholly on the circulation as a process obstructing the return of blood to the heart comparable to the effect of chronic constrictive pericarditis and is not a factor causing myocardial strain or failure except in very rare congenital cases

Symptoms and signs Tricuspid valve disease usually causes neither symptoms nor distinctive clinical signs If it is considerable there may be suggestive signs and rarely conclusive evidence if not masked by complicating factors like mitral disease and heart failure

Tricuspid stenosis of high degree may give rise to a middiastolic murmur heard maximally at the lower end of the sternum but usually distinguishable with difficulty if at all from the more marked mitral stenosis murmur transmitted from the apex in very rare cases the two different murmurs may be sharply localized or the tricuspid murmur may be preponderant Other corroborative signs of tricuspid stenosis are right atrial enlargement (see Figure 120 page 651) increased jugular venous pulse (*especially a marked chronic deep systolic jugular pulse* in the absence of an irreversible tricuspid ring dilatation) liver pulsation in the absence of other evidence of congestive failure and fluoroscopically enlargement and pulsation of the superior vena cava and unusually clear lung fields with a tendency of the esophagus to be deviated to the left by the enlarged right atrium (superimposed on the big left atrium which in marked mitral stenosis more often displaces the esophagus to the right) The increased systolic pulsation of neck veins vena cava and liver is of course due to tricuspid regurgitation but in the absence of pure dilatation of the tricuspid ring this means tricuspid valve deformity more often in the form of a diaphragm causing both stenosis and regurgitation Almost invariably atrial fibrillation is present so that the jugular and liver pulses show only ventricular waves but in very rare cases normal rhythm persists and a very large *a* wave due to the contraction of the powerful and obstructed right atrium is seen in the neck veins as a striking phenomenon (Puddu 1951)

Tricuspid regurgitation due to valvular disease is more likely than is functional regurgitation due to heart failure to show a systolic murmur localized at the lower end of the sternum because in the former case the strength of

the ventricular contraction is greater and the tricuspid ostium does not tend to remain so wide open during systole In the rare cases of well marked tricuspid regurgitation without heart failure the jugular and other venous pulses are especially pronounced with greatly exaggerated *c* or ventricular contraction waves without the sustained stasis waves uniting the *c* and *v* waves (see Chapter 8) It is important not to confuse the deep systolic jugular pulse with vigorous carotid arterial pulsation an error frequently made Fluoroscopically the superior vena cava and the right atrium are seen to pulsate markedly especially at the time of ventricular systole Finally, the liver pulse is likely to be more marked than with any other conditions it shows a great preponderance of the ventricular wave Pulsation of the spleen also has been noted (Sutton and Rawson 1935) But there may be neither hepatic nor splenic pulsation evident clinically in proved cases of tricuspid stenosis Other studies such as arterial blood pressure measurement and electrocardiography are of little or no value in the diagnosis of tricuspid valve disease the electrocardiogram almost invariably shows right ventricular preponderance due to the mitral stenosis also present

The course and prognosis, complications, and treatment of tricuspid valve disease are somewhat similar to those already noted in the discussion of mitral valve disease and in fact are almost invariably dependent on them since the mitral lesion is usually greater in degree and far more important There are however two qualifications necessary in the first place the presence of tricuspid valve disease of importance signifies a higher degree of heart disease than when mitral or mitral and aortic valve disease is present without tricuspid valve deformity and so death comes considerably earlier (averaging in Cooke and White s series only 23 years in contrast to 42 years for all the rheumatic heart cases) and in the second place after systemic venous congestion has set in life lasts longer in the cases with tricuspid stenosis than in those without, due to the protection of the heart and lungs by the mechanical obstruction of the stenosed valve from engorgement with blood Thus well marked tricuspid stenosis acts much as does chronic constrictive pericarditis in causing an invalid or semi invalid life for years with little dyspnea but with *big liver and ascites often requiring paracentesis or diuretics* in contrast to the much shorter life of the patient with pure mitral stenosis after congestive failure has once set in However there is no advantage at all in this for not only does the tricuspid patient have a longer spell of congestion but he lives a considerably shorter life than does the mitral case The younger tricuspid patients who die succumb as a rule as do the younger mitral ones to the myocardial effects of recurrent active rheumatism Surgical repair of deformed tricuspid valves has not yet been attempted so far as I am aware

The differential diagnosis of tricuspid valve disease is very difficult and has been referred to above stenosis of this valve may be indistinguishable from mitral stenosis while organic tricuspid regurgitation may give signs that easily lead to an incorrect diagnosis of mitral regurgitation with functional tricuspid regurgitation caused by right ventricular dilatation The rare irreversible dilata

tion of the tricuspid ring with little or no myocardial failure and without any tricuspid valve deformity (Fischer 1933) may be indistinguishable from tri cuspid valve disease Chronic constrictive pericarditis can be easily distin guished by the absence of any evidence of organic valvular disease in that condition

D PULMONARY VALVE DISEASE

Congenital stenosis of the pulmonic valve or of the right ventricular out flow tract (infundibulum) below it is one of the most important and interesting of all valvular defects Although uncommon it has lately held the limelight Other pulmonary valve lesions congenital or acquired are very rare The other valves are usually normal when the pulmonary valve is deformed

Etiology The causes of pulmonary valve disease are as follows first congenital stenosis or atresia the former (stenosis) with or without septal defect the latter (atresia) always with such defect second rheumatic infection which though it may attack the pulmonary valve acutely very rarely leaves any de formity third acute and subacute bacterial endocarditis

When pulmonary regurgitation is found it is almost always functional in character and due to greatly increased pulmonary arterial blood pressure and pulmonary artery dilatation resulting most commonly from advanced mitral stenosis

Pathology The usual pulmonary valve lesion of congenital nature consists of a fusion of the cusps generally into a diaphragm with a small opening in the middle of it a high degree of stenosis resulting In some cases this lesion appears to be the result of a fetal endocarditis Normally the circumference of the adult pulmonary valve should measure 8 to 9 cm it should be considered too small if it measures 6 cm or less Rarely the cusps may be defective or absent so that regurgitation results In some instances the base of the valve is a part of a narrow canal caused by faulty fetal development The pulmonary artery itself may be smaller or larger than normal or it may be of normal caliber generally it is considerably enlarged when there is pulmonary valve stenosis

In many of the cases of so called congenital pulmonary stenosis the pul monary valve itself is normal or simply of small size without other deformity the stenotic lesion being located in the region of the infundibulum of the right ventricle 2 or 3 cm below the valve and often separated from it by a cavity of variable size This should actually be called infundibular stenosis In such cases there is usually an interventricular septal defect and often dextroposition of the aorta giving rise (with right ventricular hypertrophy) to the commonest adult lesion associated with the morbus caeruleus or maladie bleue namely the tetralogy of Fallot (see Chapter 13)

An abnormal number of cusps two or four sometimes comes from fetal maldevelopment and a very rare congenital defect is valvular deficiency with regurgitation resulting

Acquired organic pulmonary regurgitation is rare and usually due to bacterial endocarditis complicating congenital heart disease pathologically it resembles bacterial endocarditis of the aortic valve

Aschoff bodies have been found in the pulmonary valve in active rheumatic heart disease but it is rare for the rheumatic infection to result in any actual deformity of the pulmonary valve

The effect of pulmonary valve lesions on the heart The effect of pulmonary valve lesions is primarily on the right ventricle causing hypertrophy and in the case of regurgitation and of failure dilatation also The largest right ventricle is found with congenital pulmonary stenosis its weight often exceeding that of the left ventricle and even reaching a figure three times the normal in such a case the cardiac apex is made up more by the right ventricle than by the left (Figure 64 page 299) The myocardium strongly hypertrophied is usually healthy but it may eventually fail under the strain of the valvular defect The right atrium also is as a rule enlarged with pulmonary valve disease

The effect of pulmonary valve lesions on the pulmonary artery Infundibular stenosis of congenital origin generally a part of the tetralogy of Fallot is accompanied by a pulmonary artery and circulation of smaller caliber than normal unless there are other congenital defects giving rise to dilatation of the artery On the other hand pulmonary valve stenosis and pulmonary regurgitation are attended by some dilatation of the artery most marked of course in the functional cases when the arterial dilatation precedes the valvular deficiency

Symptoms and signs There are no symptoms of pulmonary valve disease apart from those of associated conditions such as congenitally defective circulation, bacterial endocarditis, and heart failure There are a few characteristic signs

Pulmonary stenosis gives a harsh systolic murmur accompanied by a palpable thrill maximal in the second intercostal space just to the left of the sternum this murmur with thrill is diagnostic if aortic stenosis patent ductus arteriosus interventricular septal defect and aortic aneurysm can be excluded such exclusion is usually an easy procedure Cardiac enlargement is not marked when it involves the right ventricle but physical examination and roentgen ray study often show an increase of dullness and shadow transversely to the left sometimes giving the characteristic coeur en sabot shape of marked right ventricular preponderance with decreased pulmonary vascular shadows. The electrocardiogram shows the highest degree of right ventricular preponderance found in any condition with abnormally large *P* waves due to the right atrial enlargement (Figure 73 page 320) If a congenital ventricular or atrial septal defect is also present there is cyanosis often of high degree as in the tetralogy of Fallot In the markedly cyanotic cases polycythemia and clubbing of the fingers are evident (see Chapter 13)

Pulmonary regurgitation whether due to structural valve defect or functionally produced by pulmonary hypertension and pulmonary artery dilatation gives a blowing early diastolic murmur along the left sternal border that can

not always be distinguished in site time and character from that due to aortic regurgitation it tends to begin higher up however and often follows immediately after a greatly accentuated pulmonary second sound The distinction between pulmonary regurgitation and aortic regurgitation must some times be made by other characteristics than the murmur itself but there may be no clues in the case of very slight lesions except when the defect is functional the big pulmonary artery and perhaps also marked mitral stenosis being evident When the pulmonary regurgitation is pronounced a visible pulsation is evident in the second left interspace and vigorous pulsation of pulmonary artery right ventricle and pulmonary hilus shadows is seen fluoroscopically The pulmonary second sound is usually increased with regurgitation if the valve cusps are not badly damaged and it is decreased or absent with stenosis

Course and prognosis The course and prognosis of pulmonary valve lesions depend on the extent of the lesions With considerable congenital stenosis and much cyanosis life is usually short although there are rare instances on record of patients surviving to middle life or to early old age having lived useful active lives The lesser grades of stenosis without cyanosis are less serious I have followed for many years a frail woman cyanotic since early childhood with clubbed fingers and all the signs of pulmonary valve stenosis who finally died in the year 1949 of right heart failure at the age of 75 years She showed at postmortem examination marked pulmonary valve stenosis and an atrial septal defect She survived 18 years longer than the oldest case with these defects previously recorded Although the very rare cases of pulmonary regurgitation due to valvular disease are under considerable strain they may support moderately active lives for years Patients with functional pulmonary regurgitation do badly usually living but a few months or a year or two at best the valve not being itself responsible for the bad prognosis as it is merely a part of the terminal stage of marked mitral stenosis or pulmonary heart disease Death that may ensue in some cases of subacute or acute bacterial endocarditis is due not to the pulmonary valve involvement if present but to the active infection itself

Complications The chief complications of pulmonary valve disease are right ventricular failure and subacute bacterial endocarditis Disease of other heart valves may infrequently be associated with important lesions of the pulmonary valve rarely all four valves are involved in rheumatic heart disease

Treatment In the last edition of this book (1944) I stated that there was no special treatment for pulmonary valve disease surgical or medical but that the victim should be protected from overexertion and infection the underlying disease treated if possible and complications cared for During the years that have intervened however two surgical procedures have been introduced in treatment the first consisting of arterial anastomosis between the aorta or its branches and a pulmonary artery to bring blood to the lungs to be oxygenated thus by passing the stenosed pulmonary valve ostium in cases of the morbus caeruleus in particular the tetralogy of Fallot (Blalock and Taussig 1945

Potts 1946) and the second consisting of cutting the stenosed valve itself (Brock 1948) (see Chapter 13 for details)

E COMBINED VALVULAR DISEASE

There is no need of any particular discussion about disease of two or more valves in the same case The etiology, pathology signs, and treatment are as outlined for the individual valve lesions The course and prognosis are naturally more serious the more valves there are involved provided the degree of damage to the individual valves is comparable there is no exception in the case of well marked tricuspid stenosis which at one time was thought to improve the prognosis of other valve lesions with which it is associated before carefully collected data corrected the error which had arisen from comparison of the duration of congestive failure' in the cases with and without tricuspid stenosis (see above under Tricuspid Valve Disease) The commonest valve disease combinations are mitral plus aortic and mitral plus tricuspid (see Chapter 24) In about three quarters of all cases with combined valvular disease the mitral lesion is the essential and controlling one and in the other quarter the aortic valve defect requires the chief consideration

F INTRACARDIAC THROMBOSIS

Intracardiac thrombosis is a common complication of many cardiac conditions stasis, old scarring of the endocardium infection and infarction it was found post mortem in 265 or 34 4 per cent of 771 consecutive adult autopsied patients who died of heart disease (Garvin 1941) It is almost always bland but as in bacterial endocarditis may become infected itself It is nearly always attached to the wall of one of the heart chambers loosely or tightly constituting a *mural thrombus* in left ventricle left atrium right atrium or right ventricle or in more than one chamber free or *ball thrombi* are rare being found in a few cases of mitral stenosis in the left atrium where they may mechanically seriously obstruct the circulation even causing attacks of syncope and marked feebleness of the pulse with acrocyanosis and in extreme cases purpura and gangrene of the extremities toes fingers and ears Pedunculated thrombi in the left atrium may act much like ball thrombi A unique case of a ball thrombus in the right atrium has also been reported it was correctly diagnosed ante mortem (Wright et al 1944)

The commonest cause of mural thrombi in the heart is myocardial infarction fresh or old involving almost always the left ventricle and responsible for occasional peripheral arterial embolism to eye brain kidney mesentery arm or leg Rheumatic heart disease ranks second with thrombosis on the wall of the left atrium or in its appendage especially in the presence of atrial fibrillation which so commonly complicates mitral stenosis Bacterial endocarditis, subacute or acute is next most common as a cause of important intracardiac thrombosis in such cases located chiefly on the valves Large emboli may be ejected from the heart in either rheumatic heart disease or subacute bacterial

endocarditis Intracardiac thrombi may be found also in coronary heart disease without infarction hypertensive heart disease, and aortic valve disease syphilitic or rheumatic especially if the left ventricle and left atrium are dilated it is rare in congenital heart disease and in the cor pulmonale It is common for a mural thrombus to be laid down in successive layers in a cardiac as in an aortic aneurysm the deeper layers slowly undergoing organization and incorporation in the endocardium itself Anticoagulant therapy carried on for months or even years under close supervision may be very helpful in reducing the incidence of peripheral embolism from intracardiac thrombosis

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CHAPTER 27

PERICARDIAL DISEASE
ACUTE AND CHRONIC PERICARDITIS WITH AND WITHOUT CONSTRICTION

Pericardial disease which has been recognized longer than any other pathologic cardiac condition (its recognition dates back to the Middle Ages) has continued since the last edition of this book to be the subject of clinical investigations which have led to important advances in its diagnosis and treatment

Disease of the pericardium is a common condition occurring less often as an isolated lesion than as a part of acute heart disease especially rheumatic carditis and cardiac infarction or as a part of a polyserositis (with pleuritis or peritonitis) or of a systemic disease like septicemia or carcinomatosis It may be serious in itself or merely an incident in other serious often fatal diseases or it may be wholly unimportant It is found in about 5 per cent of postmortem examinations and is present as an acute condition in one half to two thirds of these cases A survey made of 8 912 necropsies at the Mayo Clinic (Smith and Willius 1932) showed pericarditis in 373 cases (4 2 per cent) 215 (58 per cent) of these 373 cases had acute pericardial disease 113 with effusion and 102 fibrinous without effusion the latter including 40 instances of terminal pericarditis 158 (42 per cent) had chronic pericarditis among which 15 cases had simply small localized patches ("milk spots" or "soldiers patches") A more recent survey of 13 353 consecutive autopsies done in the Los Angeles County Hospital during a period of seven years (1940 to 1946 inclusive) revealed 729 cases (5 4 per cent) of pericarditis nonspecific idiopathic pericarditis was the most frequent type found with rheumatic pericarditis next tuberculous and pneumonic pericarditis were decreasing in frequency (Griffith and Wallace 1949)

Disease of the pericardium is best considered under three headings acute pericardial disease chronic pericarditis and congenital defects

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The more virulent infect ons like pneumonia are likely to cause a purulent rather than a serous effusion

Purulent pericarditis in which a variable amount of pus is found in the pericardial sac is a complication of disease produced elsewhere in the body by pyogenic bacteria such as pneumococci staphylococci and streptococci It may be of hematogenous origin or it may be produced by direct extension from an empyema or a mediastinal abscess It is sometimes difficult to say whether such pericarditis is purulent or serofibrinous when the effusion is not frankly composed of pus but contains a suspension of cells which are largely polymorphonuclear leukocytes Of a series of 300 fatal cases of pneu monia in an army base hospital 24 per cent showed acute pericarditis mostly of purulent nature (Stone 1919) but this is now becoming rare due to specific therapy with penicillin and other curative agents

Hemorrhagic pericarditis in which the exudate is largely bloody may be caused either by infection such as tuberculosis or fulminating rheumatic fever or by malignant disease This should be distinguished from *hemopericardium* due to hemorrhage into the pericardium the result of rupture of aortic or heart wall or of coronary vessel caused by infarction aneurysm or trauma

A rare cause of acute pericardial involvement is *malignant disease* generally metastatic but sometimes penetrating the pericardium from adjacent new growth in the mediastinum Sarcoma and carcinoma are the commonest lesions of this sort (Figure 118 page 594) but many varieties of new growths have been found secondary invasion of the pericardium is much more common than a primary tumor (see Chapter 23)

Still more rare is *pneumopericardium* due to the entrance of air from a pneumothorax from esophageal or bronchial perforation or from faulty paracentesis Rarely air has been intentionally introduced into the pericardial sac in the treatment of tuberculous effusion

Age Acute pericardial disease may occur at any age in accordance with the etiologic factors it is in general most common in youth when important infections are most frequent The majority of cases occur between the ages of 10 and 40 with an average of about 25 years

Sex There is a male sex preponderance in acute pericardial diseases of nearly 3 to 1 the cause for this is not clear (Cabot 1926 Smith and Willius 1932)

Pathology *Acute fibrinous pericarditis* consists of infiltration of the peri cardium with many mononuclear and polymorphonuclear cells and a more or less adherent layer of fibrin containing such cells covering a part or the whole of the pericardium starting on either the visceral or the parietal surface but as a rule eventually involving opposite surfaces Pericarditis due to infarc tion is usually limited to the area of necrosis in contradistinction to the general involvement of the pericardium by infection The exudate may be composed of a thin or a thick layer sometimes it is very massive even a centimeter or more in thickness It tends especially when thick to have an irregular uneven surface with stringy shredded masses of fibrin projecting like fur or complexly

interwoven such irregular surfaces have been termed shaggy or bread and butter pericarditis (Figure 134) A certain amount of increase of fluid in th pericardial sac (which normally contains 25 to 50 cc) is commonly found with fibrinous pericarditis When the inflammatory or irritative proce s under goes resolution and repair there may be left only a slight thickening of the pericardium local or general But when the acute process is marked in degree or extent adhesions partial or complete between the visceral and pariet l

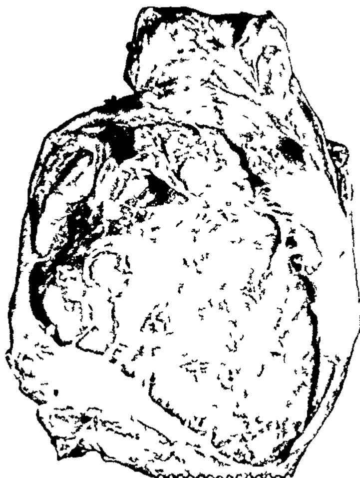


FIG 134 Photograph of heart in a boy of 12 showing acute fibrinous pericarditis in case of advanced pyelonephritis of left kidney congenital atresia of right kidney and uremia (Kindness of Dr Benjamin Castleman Massachusetts General Hospital Bo ton)

pericardial surfaces are common and if the inflammatory reaction has been deep the heart may be firmly anchored to diaphragm chest wall pleura or mediastinum or it may be encased in a firm thick unyielding scarred con tracted pericardium with little or no serous sac left both of these pericardial abnormalities may coexist in the same case

It is important to note that in practically all cases of pericarditis and particularly in those with severe involvement the subjacent myocardium is also affected it is doubtless this myocardial disease that is in the main if not wholly responsible for the electrocardiographic abnormalities in pericarditis

Serofibrinous pericarditis a type of pericardial effusion begins with fibrinous pericarditis but there is soon poured out in addition a serous exudate at varying speeds and of varying amounts from 100 up to 2 000 or 3 000 cc the latter only if the effusion is of slow development This extra fluid accumulates at first in the dependent parts of the sac but eventually it may distend the whole sac (Figures 135 and 136) unless it is withdrawn or subsides spontaneously If the amount is great there may develop extensive pressure on the surrounding structures—lungs mediastinal contents superior vena cava

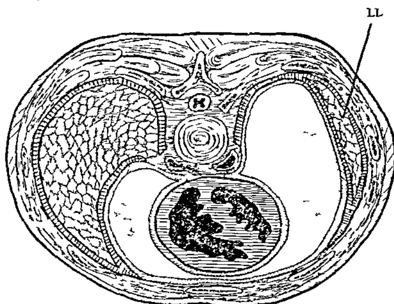


FIG 135 Diagram of cross section of thorax showing a very large pericardial effusion compressing the left lung (LL) (Conner *Am Heart J* 1926 I 431 Kindness of C V Mosby Company St Louis)

inferior vena cava and the mouths of the hepatic veins at the level of the diaphragm—along with dangerous pressure on the heart itself and on the great vessels within the pericardial sac (*cardiac tamponade*) Enormous effusions are sometimes seen usually tuberculous accumulating gradually and filling more than half the thoracic cavity In rare cases there may be a localized or pocketed pericardial effusion sometimes in unusual locations for example at the right upper border of the heart where it may simulate an aortic aneurysm such a limited effusion is the result of partial pericardial adhesions chronic or recent which prevent the effusion from taking the usual form

Purulent pericarditis (pyopericardium) If the exudate either on the surface of the pericardium or in the effusion fluid contains a great majority of poly

morphonuclear leukocytes it is called purulent, it may be thin (and watery) or thick (and creamy) and easy or difficult to aspirate

Hemorrhagic pericarditis simply signifies a high content of red blood corpuscles in the pericardial exudate sufficient to color it red, if the effusion is practically pure blood the term *hemopericardium* is employed

Neoplasms a rare cause of pericardial disease may or may not induce an effusion when such an effusion occurs it is usually bloody and may contain cancer cells



FIG 136 Roentgenograms in a case of subacute tuberculous pericarditis with effusion (*A*) Before paracentesis (*B*) after paracentesis air has been injected to take the place of some of the fluid removed Note the thickened pericardium

Symptoms Acute pericardial disease is generally painless but there are two important conditions which give rise to symptoms (1) When the pleural or outer border of the diaphragmatic pericardium is involved frequently with complicating pleurisy pain results usually sharp intermittent or continuous much aggravated by or indeed sometimes felt only during inspiration and referred to precordium left shoulder and less often to the abdomen A large part of the pericardium especially the visceral surface can be inflamed without causing pain as is usually the case with the terminal dry or fibrinous pericarditis of uremia and with the pericardial involvement in cardiac infarction (2) The other important condition giving rise to symptoms in pericarditis is distention of the pericardium by a moderate or large effusion by air or by both air and fluid With small effusions there are no symptoms with large effusions especially those developing rapidly and with extensive hemopericardium pressure symptoms may be extreme and a condition called cardiac tamponade or acute constrictive pericarditis results These pressure symptoms *are of two sorts those due to compression of the heart whereby insufficient* blood enters the heart the lungs and the systemic arteries with resulting dyspnea weakness faintness venous congestion and epigastric and right upper quadrant discomfort from hepatic engorgement and those due to compression of lungs trachea bronchi esophagus and great vessels with further dyspnea or orthopnea irritative cough hoarseness and dysphagia Distressing dyspnea and thoracic oppression are common symptoms of a large pericardial effusion and the patient often assumes a characteristic attitude of distress sitting upright and leaning forward

Signs The signs of acute pericardial disease like the symptoms are due first to the fibrinous exudate and second to the effusion The characteristic sign of acute pericarditis often found at some stage of the disease is the *friction rub* but in many cases (over 75 per cent) it is absent or escapes notice (Cabot 1926 a friction rub was heard in only 40 or 21 per cent of 186 cases of acute pericarditis) It may be heard anywhere over the precordium and sometimes when marked even in the back or neck but it is commonest along the left border of the sternum It is usually rough and grating sounding near to the ear and increased by pressure of the stethoscope but sometimes it is so soft and gentle that it is distinguished with difficulty from heart murmurs It is heard as a rule both in systole and in diastole especially in the earlier parts of each but it may be almost continuous or it may be very brief and limited to systole alone being heard perhaps during only one phase of respiration It may be transient lasting but a few hours or it may persist with little change for weeks It is often audible even in the presence of an effusion but sometimes it disappears or is dulled when an effusion develops The pericardial friction rub if marked can be felt as well as heard

The other characteristic signs of acute pericardial disease are those produced by an effusion An amount less than 150 cc is probably not discoverable by any method of examination since it produces no definite signs In fact effusions of less than 300 cc are usually missed clinically The presence of a pericard al

friction rub should cause careful search for early signs of an effusion which may appear with the friction rub or shortly after it disappears The earliest sign is roentgenologic and consists of a bulging of the lowest corners of the heart shadow because of the collection of fluid at these points it is especially well seen in the oblique views fluoroscopically As more fluid gathers it tends to fill in the hollows and grooves of the heart and great vessels rounding out their contours and obscuring and eventually abolishing the cardiac landmarks this change at first apparent by roentgen ray is later found by percussion also The cardiac shadow and area of dullness often rapidly increase with the accumulation of fluid giving rise sometimes to an erroneous diagnosis of acute cardiac dilatation The increase may be very great so that the effusion shadow and the area of dullness may extend to the left axilla (Figure 136) A characteristic change in shape of the effusion shadow occurs with change of position the shadow in the recumbent position being globular and that in the upright position pyriform (pear shaped) often obscurely likened to the shape of a water bottle This change of shape is of course due to the effect of gravity it is sometimes of considerable value in distinguishing between pericardial effusion and marked cardiac enlargement By fluoroscopy and teleroentgenography the heart shadow itself is almost invariably buried in the shadow of the pericardial effusion since the densities of heart and effusion are almost the same The cardiac pulsation fluoroscopically may be much diminished or even absent An obtuse right cardiohepatic angle of percussion dullness (Rotch s sign) is found with large effusions

An early sign of the *cardiac tamponade* or *acute constrictive pericarditis* due to pericardial effusion is enlargement of the liver with tenderness on pressure Slightly displaced downward the liver is engorged due to compression of the right atrium great veins and especially the mouths of the hepatic veins which open into the inferior vena cava caused by the resting of fluid in the pericardial sac on the diaphragm at the point where the inferior vena cava comes through Prolonged and extensive blocking of the hepatic veins may give rise to ascites with or without slight edema of the legs which is due to coincident obstruction to the blood flow in the inferior vena cava With very extensive effusions and the resulting compression of right atrium and both superior and inferior venae cavae general edema may occur but this is neither common nor marked Cyanosis of skin and mucous membranes is frequently found when the heart action is much obstructed and the jugular veins are frequently engorged with visible venous pulse in the upright position

After the development of a considerable pericardial effusion heart sounds and murmurs are often diminished and the friction rub may disappear The blood pressure with small effusions is unchanged but with large effusions the systolic pressure is decreased and the pulse pressure much diminished With acute constrictive pericarditis the pulse pressure may drop to 20 cm With very large effusions the radial pulse may almost entirely disappear and in fact sometimes does disappear during inspiration which is usually labored This exaggeration of the so-called paradoxical pulse is of some diagnostic

significance (see Chapter 8) The systemic venous pressure is often greatly elevated to 20 or 30 cm of water (normal 4 to 8 cm) Tachycardia is usual to make up for the small cardiac output per beat but arrhythmia is uncommon

The one other important sign (Ewart s sign) of a large pericardial effusion is due to compression of the left lung At the angle of the left scapula an area of variable size is frequently found over which there are dullness on percussion bronchial breathing and increased tactile and auscultatory fremitus (Ewart 1896) this may occasion an erroneous diagnosis of pneumonia Recently however it has been pointed out that in some cases at least the Ewart s sign in pericarditis is due to an associated pulmonary lesion in the left lower lobe (infarct or rheumatic pneumonia —Levine and Gevalt 1940) or more likely to an accompanying pleural effusion at the left base (as a part of a polyserositis—Gordon 1940)

Ewart described ten signs of pericardial effusion of which the eighth and tenth are as follows

Ewart William Practical Aids in the Diagnosis of Pericardial Effusion in Connection with the Question as to Surgical Treatment *Brit M J* 1896 I 717

Eighth Sign The Posterior Pericardial Patch of Dulness Whenever fluid is effused into the pericardium the normal resonance is modified at the left posterior base in a most definite way A patch of marked dulness is found at the left inner base extending from the spine for varying distances outwards usually not quite so far as the scapular (angle) line and ceasing abruptly with a vertical outer boundary Above its extension is also variable according to the size of the effusion commonly it does not extent higher than the level of the ninth or tenth rib and here again its horizontal boundary is abrupt Its shape there is that of a square and it is quite unlike that of any dulness arising from pleuritic effusion You will not experience any difficulty in identifying the patch in question Rather greater care in percussion is needed however to follow the dulness as it extends to the corresponding vertebræ and for a short distance also to the right of them For some time I had overlooked this extension which owing to the general resonance of the right base is one of partial dulness only When however the effusion is considerable the extension of the patch in the right chest may become almost absolutely dull

I wish time permitted me to discuss with you the significance and the probable mechanism of production of this singular and most helpful sign It is best I should confine myself on this occasion to practical points The value of this sign is that unlike many others it is very sharply defined and does not fit any other diagnosis When in a doubtful case all the signs observed in front support the diagnosis of effusion and this sign is also found we have then in hand complete and crucial evidence of the existence of fluid whilst when as sometimes occurs previous adhesion of the anterior surface of the heart to the chest wall renders diagnosis extremely difficult this help is invaluable and its place so far as I am aware cannot be supplied by any other available diagnostic method

Tenth Sign The Posterior Pericardial Patch of Tubular Breathing and Ægophony Immediately below or slightly to the left of the tip of the left scapula a patch of about 2 inches in diameter presents well marked tubular breathing and—

ægophony This sign although not so important as that of the patch of dul ness is very commonly if not always present in cases of considerable effusion, and gives valuable confirmation to other signs It has been described by other observers The mechanism of its production is analogous to that suggested above and is doubtless connected with pressure on the bronchi descending to that district, and with partial collapse of the pulmonary tissues It also occurs in pleural effu sions

Other signs such as fever and leukocytosis may or may not be present de pending on the cause of the acute pericardial disease, they are generally present at some time during the illness

Electrocardiography is of distinct diagnostic value changes in the *S T* seg ments and *T* waves and low voltage of all complexes being frequently found with extensive acute pericarditis with or without effusion the more marked the pericarditis the more abnormal the electrocardiogram especially if there is a long drawn out course or a large effusion The *S T* segment and *T* wave changes in the precordial and limb leads resemble to a certain extent those found in coronary heart disease especially those in acute occlusion over the site of infarction namely elevation of the *S T* segments with succeeding flattening or inversion of the *T* waves there are however two distinct differ ences (1) the same *S T* segment and *T* directions are usually consistently found in all three classical limb leads in contrast to their opposite directions in Leads 1 and 3 in myocardial infarction and (2) the *QRS* waves are not affected as a rule in pericarditis as they tend to be after acute coronary occlu sion In the chest leads the *T* waves in acute pericarditis are often inverted Sometimes the electrocardiogram returns to normal rapidly with subsidence of the acute pericarditis (Figure 137) but often some of the abnormality persists even though the patient feels well The electrocardiographic changes in acute pericarditis have been ascribed to two factors compression of the coronary arteries by effusion or exudate and involvement of the underlying myo cardium the latter is almost certainly the more important if not the only cause An interesting electrocardiographic distinction between massive pericardial effusion and marked cardiac enlargement has been pointed out by Tung (1941) the duration of electric systole (*Q T* interval) is normal in the former and prolonged in the latter

Paracentesis of the pericardium may prove the presence of fluid when there is an effusion but such confirmation is unnecessary except when pus is sus pected or the procedure is an essential part of treatment

With air and fluid together in the pericardium a tinkling splash may be heard with each heartbeat

Course and prognosis Acute pericardial disease generally occurs either as a benign illness discovered on occasion in the course of a fever and clearing spontaneously without sequelae in the course of days or weeks or as a pass ing complication of some infection like rheumatic fever or other illness like uremia or cardiac infarction It may not be of great importance in itself the fibrinous or serofibrinous involvement subsiding spontaneously or occurring

simply as a terminal event in a fatal disease Frequently the pericarditis does not even produce symptoms or signs but is discovered only at postmortem examination There are however three conditions in which the acute pericardial involvement is itself of great immediate importance One is the infrequent very serious purulent pericarditis which is usually secondary to disease else where and may be fatal unless there is ample surgical evacuation and drainage of the pus together with specific penicillin or sulfonamide therapy and good resistance on the patient s part The second is a pericarditis that initiates a grave miliary tuberculosis The third is more frequent viz. a large pericardial effusion generally of tuberculous origin but sometimes of rheumatic or of unknown etiology which causes serious pressure symptoms and signs (acute constrictive pericarditis) and which may endanger life unless it is aspirated But as a rule drainage is unnecessary in acute pericardial disease

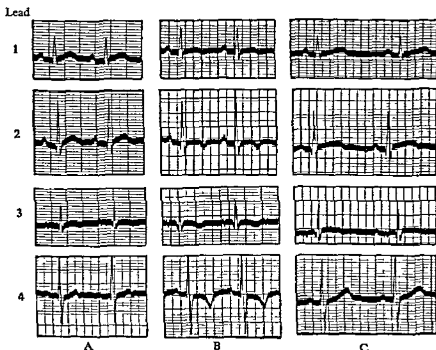


FIG 137 Electrocardiograms (four leads) of H C a lad of 12 years of age at the beginning of during and after recovery from acute pericarditis (*A*) Sept 4 1942 (*B*) Sept 8 1942 (*C*) Sept. 25 1942 Note especially the late inversion of the *T* waves in *B*

The onset of acute pericarditis is likely to be rapid but it is often masked by the underlying illness and not considered until discovered in the course of physical examination or roentgen ray study Occasionally pain calls attention to an acute pericarditis which seems to appear out of a clear sky The dura tion of the pericardial involvement in its acute stage varies from a few days to

a few weeks but chronic pericarditis may result Such chronic pericarditis may cause no trouble at all or it may produce symptoms and signs after the lapse of some months or years

The immediate prognosis in acute pericarditis is good as a rule in the non pyogenic and nontuberculous infections in spite of well marked symptoms and signs but the total mortality is still fairly high because the term acute pericarditis includes the terminal pericarditis of uremia and overwhelming septic infections occasional cases of fatal cardiac infarction and rare cases of death due to the mechanical effect of a huge or rapidly developing effusion The introduction of penicillin and sulfonamide therapy has materially lowered the mortality in the cases with septic pericarditis during the last few years (see below under Treatment) Tuberculous pericarditis is often fatal of one series of 24 cases of proved tuberculous pericarditis admitted to the Vanderbilt Hospital in Nashville Tennessee during a period of eleven years only 4 survived (Blalock and Levy 1937) and analyses of other series of cases by Keefer (1937) and by Heimann and Binder (1940) have also indicated a generally poor prognosis although streptomycin has apparently been helpful or even curative in a few cases and it is also quite possible that cases too mild to diagnose may recover or lead to chronic constrictive pericarditis

Hydropericardium a part of general anasarca due to heart failure or nephritis is not an important condition in itself the course and prognosis naturally depending on the underlying disease it does not become large enough to constrict the heart

Complications The acute pericardial disease is itself but a complication of infections such as rheumatic fever and tuberculosis or of other diseases like uremia and coronary thrombosis It rarely produces complications of its own except for the establishment of pericardial effusion and adhesions Pleuritis may follow pericarditis by contact infection though usually the reverse is the sequence Commonly associated with acute pericarditis are nephritis valvular disease and polyserositis

Treatment The treatment of acute pericardial disease is wholly that of the underlying cause—rheumatic fever tuberculosis purulent pericarditis coronary thrombosis or other disease—except for two conditions pain and very large pericardial effusions

Pain should be relieved by morphine when it is very severe for lesser grades of pain salicylates bromides or codeine may suffice An ice bag placed comfortably over the precordium may be received gratefully by the patient

The pain of acute rheumatic pericarditis is often much relieved by salicylate administration which probably also helps in the resolution of the acute process including the effusion

For acute tuberculous pericarditis streptomycin has been tried during the past few years with benefit in some cases by injection intramuscularly (1 to 2 gm daily) and also by intrapericardial instillation although of course with the risk of labyrinthitis

If pericarditis develops in the course of a pyogenic infection or following it and is itself the cause of prolongation of the illness or of accumulation of peri

cardial fluid exploratory paracentesis should be done as soon as possible or better still to save time and the patient s strength surgical pericardiostomy if the diagnosis of purulent pericarditis seems reasonably certain Equally im portant is the administration of penicillin 300 000 units daily or the sulfonamides e g sulfadiazene 1 gm 4 to 6 times a day Cure is now possible in many such cases which in former days were rapidly fatal

If the pus is thick it will be necessary to use a large aspirating needle or trocar sometimes only an incision will permit ready removal of the pus The discovery of a definite purulent pericarditis demands surgical interference at once with drainage as in the case of empyema and care should be taken that the bottom of the pericardial sac be drained Recovery is possible in such cases if proper treatment is instituted early in the disease If in the development or course of a pericardial effusion symptoms or signs (especially a rapid fall in arterial and pulse pressure and a rapid rise in venous pressure) indicate the existence of a high and perhaps dangerous intrapericardial pressure (cardiac tamponade or acute constrictive pericarditis) the pericardium should be aspirated of at least several hundred cubic centimeters of fluid provided they are easily withdrawn without inducing disagreeable symptoms As much as 1 000 or 1 500 cc of fluid have been aspirated in some cases The removal of even a small percentage of a large effusion may suffice to relieve distressing orthopnea and thoracic and epigastric oppression hypotension and small pulse with the saving of life and induction of convalescence

Pericardial paracentesis may be done in everal ways It is often convenient to employ a long needle of small or average caliber (1 mm) attached to a large syringe of 50 or 100 cc capacity by rubber tubing directly or through a three way connection which allows the fluid to be aspirated and discharged without disconnecting the syringe the direct connection is somewhat more convenient since the syringe can be easily removed and the fluid quickly ejected each time after the syringe has been filled the rubber tube being closed by finger or clamp pressure while the syringe is disconnected In rare cases a larger caliber needle (2 mm bore) may be necessary

The site at which the pericardium should be tapped need not be limited to one spot for at times the fluid is more or less localized by previous adhesions and in some cases it is more easily obtained in one place than in another Generally the best site to try first is the fifth left intercostal space 1 or 2 cm toward the sternum from the left outer border of percussion dullness and roentgen ray shadow and therefore in the case of a large effusion usually beyond the position of the apex or left border of the heart The skin and sub cutaneous tissues should be anesthetized first conveniently with 2 or 3 cc of 0 5 per cent procaine (Novocain) solution using a small syringe and needle this local anesthesia which is often omitted or is inadequately done is wise for two reasons in the first place for the comfort of the patient especially since two or more attempts are sometimes necessary before the effusion is reached and secondly for the greater convenience of the physician who does not need to hurry or to fear a sudden movement of the patient such as may occur if sharp pain is felt After a few minutes wait for the anesthesia to take

effect, the exploratory needle is inserted pointed back and inward toward the spine and forced slowly between the ribs until it is felt to penetrate the resistant pericardial membrane at a variable distance from the outer surface of the thorax depending on the thickness of the chest wall but averaging 3 or 4 cm in the nonobese adult male When the pericardial sac is entered fluid may or may not be easily withdrawn depending on the thickness of the fluid the caliber of the needle or trocar the position of the trocar in relation to the fluid and whether or not obstruction of the mouth or lumen of the trocar results from a fragment of fibrin or from pressure against heart wall or pericardial surface If no fluid comes the needle should be variously tilted slightly withdrawn or inserted further or completely withdrawn to be introduced again Occasionally the heart itself is felt against the trocar and may move it at every contraction this should not cause alarm for even perforation of the ventricular wall is not dangerous except in rare cases when the right ventricle or right atrium is badly traumatized or a large coronary vessel may be injured If fluid is not found by paracentesis well out in the fifth left interspace another trial may be made in the fourth or fifth interspace nearer the sternum or in the fourth interspace to the right of the sternum and just inside the right border of dullness or roentgen shadow This last location is a favorable one when the effusion projects unusually far to the right I have aspirated 600 cc of fluid from this site when adhesions prevented fluid accumulation to the left

There are two other sites for pericardial paracentesis that have been tried and sometimes found favorable the epigastrium and the left side of the posterior thoracic wall The epigastric site is advantageous because it drains the lower part of the pericardial sac but special anatomic knowledge and experience are necessary so that the needle will be directed upward at the proper angle as well as backward and inward In this method the needle is inserted high up in the sharp angle between the ensiform cartilage and the left costal border and is pointed upward at an angle of about 30 to 40 degrees to avoid peritoneum and diaphragm the pericardial sac being encountered at a depth of about 3 or 4 cm The left posterior thoracic site is useful in rare cases in which fluid is not obtained by paracentesis in the usual positions but is almost certainly present as indicated by pulmonary pressure signs at the angle of the left scapula (Ewart s sign) provided one can rule out pulmonary consolidation or pleural effusion as a cause of the Ewart s sign not always easy to do With the left arm of the patient raised to move the scapula outward the needle is inserted after local anesthetization in the seventh or eighth intercostal space in the midscapular line Insertion to the depth of 5 to 8 cm should yield fluid from a distended pericardial sac I have withdrawn 500 cc of pericardial fluid through the back affording great relief to the patient when attempts through the anterior chest wall were unsuccessful and the need of pericardial paracentesis was urgent There is no danger of pleural or lung infection by this procedure unless purulent pericarditis is present in which case this site for the paracentesis should of course be avoided

Aspiration of the pericardium usually does not have to be repeated either

the serous effusion soon subsides or operation with drainage, is carried out for purulent pericarditis In a few cases however especially those of tuberculous origin it may be necessary to aspirate several times usually at intervals of a week or two or in severe cases at intervals of a few days

Sometimes the pericardial sac is partially filled with air intentionally after fluid has been removed (Figure 136 page 712) with the idea of allowing resolution of the acute pericardial inflammation to occur with less likelihood of the formation of crippling adhesions during convalescence but this procedure has not yet proved to be particularly successful

Acute pericardial tamponade due to hemorrhage from trauma needs rapid relief by surgery to repair the heart wound along with transfusion of whole blood Intravenous infusions have been found beneficial preoperatively in acute pericardial tamponade (Cooper et al 1944)

Differential diagnosis Acute pericardial disease is often missed altogether because of absence or inadequacy of symptoms or signs predominance of the underlying disease or hasty or careless examination There are four conditions which are most likely to be confused with acute pericardial disease (1) cardiac enlargement (2) acute myocardial infarction (3) the presence of harsh heart murmurs and (4) acute abdominal disease

The fast development of pericardial effusion the frequent presence of a friction rub and the absence of particular reason for sudden cardiac dilatation generally distinguish without difficulty pericardial disease from cardiac enlargement but in some cases the distinction is impossible and in still other cases there is a confusing combination of pericardial effusion and cardiac enlargement in the same individual The electrocardiogram is often helpful in the differentiation

The frequent possibility of the confusion of acute infectious pericarditis especially the idiopathic kind in young male adults with cardiac infarction has become increasingly evident of late years and the importance of this error especially as regards prognosis can hardly be overemphasized The prolonged and often severe precordial pain fever leukocytosis pericardial friction rub and common appearance of abnormalities in the electrocardiogram in acute infectious pericarditis may easily simulate the findings in acute cardiac infarction There are certain clues however in the differentiation of the two conditions chief of which is the fact that infectious pericarditis itself is almost invariably painful with much aggravation of the pain on inspiration due in part to the common coexistence of a pleuritis (in fact the process is as a rule really a pleuropericarditis) while the pericarditis associated with myocardial infarction is per se (being visceral) painless the severe pain of the muscle involvement being uninfluenced by respiration and subsiding as a rule by the time the friction rub appears Other clues are the difference in the electrocardiograms (see above) the frequent development of some degree of pericardial effusion and the younger age of the majority of the cases of acute pericarditis

Very rarely does the character of the pericardial friction rub resemble that

of a heart murmur but it may be necessary in a few cases to wait to see if the uncertain sound persists disappears or becomes more definitely one thing or the other

Pain of acute pericarditis referred to the abdomen or hepatic engorgement due to an acute or subacute pericardial effusion may occasion a mistaken diagnosis of acute abdominal disease especially in children laparotomy has been done in some such cases for supposed acute appendicitis or other lesion

Rare causes of mistaken diagnoses include localized or encapsulated pericardial effusions which may be taken for aortic aneurysm mediastinal tumor or dilated left atrium, a pleural friction rub may be wrongly called pericardial. Careful study generally simplifies the differentiation

B CHRONIC PERICARDITIS INCLUDING CHRONIC CONSTRICTIVE PERICARDITIS (PICK S DISEASE)

One of the most difficult of all clinical cardiovascular diagnoses is that of chronic pericarditis Fortunately it is for the most part of little or no importance Frequently it produces neither symptoms nor signs

Etiology *Cause* The causes of chronic pericarditis are acute pericardial inflammation of rheumatic tuberculous septic or other often unknown infectious origin and cardiac infarction (from coronary thrombosis) neoplasms and hemopericardium from trauma The commonest known cause is the rheumatic infection and next comes pulmonary and pleural disease Often the cause is obscure the antecedent acute inflammation having escaped notice On occasion tuberculosis pneumonia polyserositis (Concato s disease Concato 1881) and the influenzal infection and rarely some septic infection are known to be responsible for chronic pericarditis Trauma resulting in hemopericardium may leave chronic adhesive pericarditis

At the Mayo Clinic (Smith and Willius 1932) 144 cases of chronic adherent pericarditis were found among 373 cases of pericardial disease (38 4 per cent), rheumatic fever was apparently the etiologic factor in 21 5 per cent pulmonary and pleural disease in 17 4 per cent cardiac infarction in 6 per cent neoplasms in 2 8 per cent and tuberculosis in 2 1 per cent while in the remainder (50 0 per cent) the cause was not evident

Age Although the greatest incidence of this pathologic condition is in middle age chronic pericarditis may exist at any age between 10 and 60 years The average age is about 35 years

Sex Males are more often affected than females in the ratio of 2 or 3 to 1

Pathology Following acute pericarditis of slight degree the healing process may leave but little thickening or scarring on more or less extensive areas of the pericardial surface without adhesions between the surfaces (parietal and visceral) but when the active process is extensive or of long duration adhesions of considerable extent result Thus chronic pericarditis may be divided pathologically into five groups *First* there is simply slight scarring consisting of thickening and fibrosis of the pericardial surface usually in small areas

without adhesions and without any effect on heart size or function The well known milk spots or soldier s patches probably belong in this category although their etiology is obscure As a matter of fact pericardial milk spots are common about one third of all persons over a year old showing them at autopsy (Nelson 1940) they are scarce in children but very common in old age two thirds of individuals with chronic valvular disease have them and half of those with coronary heart disease *Second* there are slight loose localized pericardial adhesions of fibrous tissue also without effect on the size or function of the heart *Third* there are the cases of complete but not dense adhesion between the visceral and parietal pericardial surfaces without firm fixation to chest wall diaphragm or mediastinum In such cases the adhesions are often loose and the pericardium is but little thickened so that there is no handicap to the heart in its function and no cardiac enlargement *Fourth* there is *concretio cordis* (a hardening of the heart) when the pericardial adhesions are solid thickened and even calcified For such instances in which the heart function is impeded and the inflow of blood from the great veins obstructed (Figure 138 page 724) the best designation is *chronic constrictive peri carditis* this condition may follow a polyserositis of unknown cause it may result from pneumonia but in most cases it is probably of tuberculous origin Rarely the visceral and parietal pericardial layers may be densely thickened and unyielding but without complete adhesion Often in these cases the heart is adherent to the diaphragm a further handicap *Fifth* the adhesive peri carditis may be complicated by an extension of the process to the mediastinum and chest wall so that the heart itself is anchored in every direction by firm fibrous tissue (*chronic mediastinopericarditis*) with much extra work and some enlargement of the heart resulting

The factors responsible for the fourth and fifth groups that is constricting and anchoring adhesions are often present in the same case In fact it is usually difficult or impossible to separate these two groups the fourth and the fifth in general they might best be considered as one although there are exceptions The only important cases of chronic adhesive pericarditis de manding especial attention belong here

Occasionally lime and rarely even bone are deposited in chronic pericardial adhesions when they are especially thick and massive

It is of much interest that long before Pick (1896) and even before Kuss maul (1873) the effect of chronic constrictive pericarditis on the heart and circulation was well understood by Chevers (1842) and Wilks (1870) at Guy s Hospital in London

Chevers N Observations on the Diseases of the Orifice and Valves of the Aorta *Guy s Hosp Rep* 1842 VII 387

The principal cause of dangerous symptoms in cases of the above description [with much thickened constricted pericardium and obliterated sac] appears to arise from the occurrence of gradual contraction in the layer of adhesive matter which has been deposited around the heart compressing its muscular tissue and

embarrassing its systolic and diastolic movements but more particularly the latter Under these circumstances the circulation seems after a time in great measure to adapt itself to the encumbered condition of the heart The ventricles having become diminished in capacity make up for this loss by the rapidity of their con tractions (hence the small and rapid pulse noticed in the above case) while the main arteries if not already diseased adapt themselves to the dimensions of the



FIG 138 Photograph of heart encased in a thickened leathery constrictive peri cardium Case of chronic constrictive pericarditis (so-called Pick s disease)

cavities from which they arise And thus the blood passes onward for a time with tolerable freedom but the patients become incapable of continued muscular exertion and are always liable to suffer from dropsy and other serous effusions upon the occurrence of very slight pulmonary obstructions In the case which I have quoted the serous effusions which gave rise to the most prominent symptoms of disease evidently arose from the cavities of the heart being no longer capable of transmitting the blood with ordinary freedom The heart had doubtless for a long time continued to become more and more compressed weakened and embarrassed by the gradual contraction of the adventitious structure which surrounded it distension of the great veins and abdominal viscera had necessarily followed and the resulting anasarca and ascites must have added still more to the obstruction with which the already almost powerless heart had to contend

Chronic mediastinopericarditis may be at times very complicated causing obstruction of the great veins the superior vena cava inferior vena cava and even the hepatic veins by kinking and compression but particularly constriction and anchoring of the heart chambers themselves It is the hepatic vein obstruction *secondary* to the constriction of the heart itself with or without an additional factor of local blocking that leads to hepatic congestion enlargement and eventual cirrhosis called *mediastinopericarditic pseudocirrhosis of the liver* or *Pick s disease* (Pick 1896) It should be added that this last named condition may or may not be associated with polyserositis (Concato s disease) and perihepatitis (icing or frosting of the peritoneum over the liver due to chronic peritonitis) these two different conditions that is mediastinopericarditis and polyserositis have often been confused in the past since it is true that the former condition may result from the latter Chronic mediastinopericarditis may involve the superior vena cava even more than the inferior vena cava in cases of the superior mediastinal (pressure) syndrome but usually the inferior vena cava and hepatic veins are equally or more affected (inferior mediastinal syndrome) as a matter of fact the condition is usually a total mediastinal syndrome The right heart chambers are more often seriously constricted than are the left heart chambers though there are many exceptions The liver rarely shows more than vascular congestion with very little cirrhotic change a few cases progress to or are complicated by a moderate degree of hepatic cirrhosis However there are seldom if ever the marked changes found in the usual cases of portal cirrhosis

Pick F Uber chronische unter dem Bilde der Lebercirrhose verlaufende Perikarditis (perikarditische Pseudolebercirrhose) nebst Bemerkungen uber die Zuckergussleber (Curschmann) *Ztschr f klin Med* 1896 XXIX 385

Pick described three cases (including the postmortem examination) of what he called pseudocirrhosis of the liver resulting from chronic adhesive pericarditis involving the mediastinum The sex and age of these three cases were as follows male of forty seven years male of twenty six years and male of twenty four years In the third case tuberculosis was the etiologic factor behind the pericarditis in the second case tuberculosis was the probable factor and in the first case the cause was unknown

His first sentences and his conclusions I have translated as follows

To differentiate clearly between primary and secondary disease of the liver is very difficult in occasional cases where liver enlargement with more or less ascites eventually leads to cirrhosis This is especially the case if there are no well marked physical signs of a heart lesion or of circulatory stasis in the upper part of the body

Conclusions

1 There is a symptom complex of *pericarditic pseudocirrhosis of the liver* which is deceptively similar to one of the mixed forms of hepatic cirrhosis with enlarged liver and considerable ascites but no jaundice This pseudocirrhosis of the liver is caused by disturbances of the circulation of the liver due to latent pericarditis These circulatory disturbances lead to an increase in connective tissue (fibrosis or cirrhosis) which in turn causes stasis in the portal circulation with marked ascites

2 This symptom complex is found preponderantly in young individuals but it may be observed also in later periods of life

3 The following points are important in the differential diagnosis (a) absence of an etiologic factor for cirrhosis of the liver (b) history of a previous pericarditis and (c) earlier occurrence of edema of the legs Certainty can come only through subsequent examination of the heart

Symptoms There may or may not be symptoms from chronic pericarditis Usually there are none since cases of the first three unimportant pathologic groups discussed above are much more frequent than of the last two important groups Clinically chronic pericarditis may be divided into four groups (1) that with unimportant adhesions or none at all which comprises the first three pathologic groups (2) that of an important degree of constrictive pericarditis without external adhesions (3) that of significant external adhesions to chest wall and mediastinum with little or no constriction of heart or great veins and (4) that of groups 2 and 3 combined to a greater or lesser degree It is unlikely that from uncomplicated external pericardial adhesions per se the heart is ever exhausted by the strain of tugging in the chest wall or of pulling up the diaphragm with each contraction when heart muscle failure develops in the presence of adhesive pericarditis there is always to be found other more adequate cause for the failure especially aortic or mitral valvular disease the pericardial adhesions may of course add a minor burden in addition but it seems to be relatively unimportant When on the other hand the heart is so compressed that there is insufficient blood flow activity is usually much limited abdominal discomfort and distention result from hepatic congestion and ascites and there may be also dyspnea and weakness

Signs As is the case with symptoms so there may be no signs whatsoever of chronic pericarditis unless the pericardium is extensively adherent or constrictive The usual absence of important adhesions clearly explains why the diagnosis is so often missed during life

A frequent finding in chronic adhesive pericarditis is cardiac enlargement but this is inconstant and not diagnostic and almost always there are other lesions especially valvular defects that are much more *important* causes of

the enlargement Cardiac enlargement is not present unless extra work has been required of the heart because of adhesions to chest wall diaphragm or mediastinum The enlargement is due to a combination of hypertrophy and dilatation Years ago it was reported (Cabot 1926) that the largest hearts of a certain series of cases were the result of chronic pericarditis but a careful survey of these cases showed that aortic valve defects (and not the pericarditis) were the real cause of the enlargement (White Sprague and Jones 1926) Increased heart size was found in 29 (55 per cent) of a series of 53 cases of chronic constrictive pericarditis (Paul Castleman and White 1948)

There are two signs which are more or less distinctive of chronic pericarditis of the more serious types The first is the fixation of the heart by adhesions in some cases physical examination and roentgen ray study show little or no change in the position of the heart with change in body position (upright recumbent right lateral position left lateral position) or respiration (full in spiration and full expiration) Electrocardiography is of least value in studying the extent to which the heart is anchored (see Chapter 9) Fixation of the heart to the sternum causes the heart to rise rather than to descend with inspiration with retraction of the lower end of the sternum at the same time Also the fixation of the heart and pleural edges may prevent any change of pulmonary resonance over the heart between full inspiration and full expira tion The pleural edges are at times somewhat retracted from over the heart increasing the area of absolute percussion dullness Such definite fixation is however found in relatively few cases Other confirmatory signs of extensive pericardial adhesions are inconclusive in themselves they include especially a systolic retraction of the chest wall particularly in the left axillary region and left back involving the ribs as well as the intercostal spaces (Broadbent s sign) and probably due to fixation of heart to diaphragm Although this sign is sometimes also seen when the heart especially the right ventricle is very large without any adhesions it is seen best in cases of adherent pericardium

Broadbent John F H *Adherent Pericardium* London 1895

In Chapter II the section on Physical Signs of Adherent Pericardium begins as follows

The physical signs differ according as the adhesions exist only between the two layers of pericardium or between the pericardium and chest wall or adjoining pleura as well In the latter case they are more numerous and distinctive and will therefore be first discussed

P 26 *Retraction of the Posterior Lateral Portions of the Thoracic Walls* In cases of adherent pericardium marked systolic retraction of some of the lower ribs on the lateral or posterior aspect of the thorax may sometimes be seen This phenomenon is bes seen when the patient is sitting up in a good light and the movements of the chest are carefully observed from a short distance off first from the front and then from the lateral aspect When a pulsatile movement is seen over the lowest part of the left side of the chest posteriorly it may at first sight appear to be expansile On a more careful scrutiny it will be found that there is a tug on the false ribs during the cardiac systole and a sharp rebound during diastole

which can be felt as well as seen when the hand is laid flat upon the chest wall at the spot it is more marked when a deep inspiration is made it may be seen occasionally not only on the left side but also on the right especially if the patient leans over to the left

Here it is not possible that the heart can be directly fixed to the chest wall at the points of retraction by pericardial adhesions as the lung tissue intervenes but the explanation seems to be the following The heart is by means of the pericardium adherent not only to the central tendon of the diaphragm but probably also to a large area of the fleshy or muscular portion of the diaphragm and, it may be to the anterior thoracic wall as well as it contracts it drags upwards and inwards the less resistant fleshy part of the diaphragm towards the central tendon or anterior chest wall hence the points of attachment of the digitations of the diaphragm to the lower ribs and costal cartilages are dragged inwards and downwards It will always be found in such cases that the retracted positions of the chest wall correspond to the floating ribs or costal cartilages of the lower ribs at the points of attachment of the diaphragm (Systolic recession of the left subcostal angle and epigastrium does not necessarily imply the presence of pericardial adhesions)

The above is a most important diagnostic sign of adherent pericardium when present and is quite distinct from recession of the lower ribs in inspiration "

The other important and distinctive finding on physical examination occurs in cases of constrictive pericarditis due to the small amount of blood that can enter and therefore leave the heart because of the cardiac compression This finding consists of increase of systemic venous pressure even up to 20 or 30 cm of water (normal 6 to 8 cm) with engorged neck veins and hepatic engorgement (and in late cases slight cirrhosis), and ascites alone or out of all proportion to the degree of dependent edema in the legs (Figure 139) accompanied by low arterial pulse pressure often so small that the radial pulse almost disappears on deep inspiration (marked paradoxical pulse) This evidence is the clearest indication that we possess of an important degree of chronic pericarditis when linked with the finding of a relatively normal heart without valvular disease with little or no enlargement and with limited diastolic excursion as noted by roentgen ray study The pulsation of the right heart border is more often embarrassed than is that of the left

There is one sign a rare one which is pathognomonic of chronic pericarditis and that is the evidence by roentgen ray of calcification of the pericardium (Figure 140 page 730) Pericardial calcification may or may not be attended by constriction of the heart it was present in 29 (55 per cent) of 53 cases of chronic constrictive pericarditis (Paul Castleman and White 1948) Roentgen ray examination also infrequently shows actual irregularities of the contour of the cardiac shadow due to the pull of adhesions

Very helpful confirmatory evidence of chronic constrictive pericarditis is electrocardiographic There is invariably either low voltage of *QRS* waves (60 per cent) or inversion of *T* waves (all cases) or both (Figure 141 page 731) These abnormalities are also frequently found in cases of acute constrictive pericarditis

There are ordinarily no characteristic changes in heart shape and no mur murs or arrhythmias except as they develop as complications A systolic mur mur at the apex is frequent with enlargement and is due to functional mitral regurgitation Very rarely there may be also a mitral diastolic murmur at the apex without mitral or aortic valve disease due simply to left ventricular

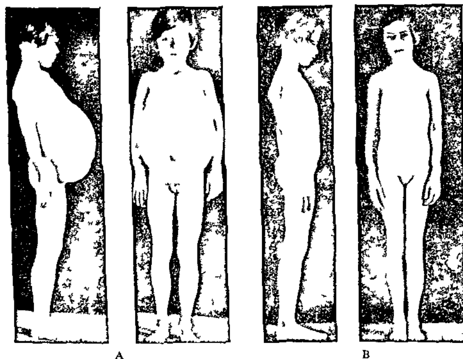


FIG 139 Photographs of young girl with chronic constrictive pericarditis (so-called Pick s disease) (*A*) during her disability (*B*) one and one half years after her surgical cure

dilatation resulting from the pericardial adhesions A frequent finding in chronic constrictive pericarditis both before and after pericardial resection is a loud third heart sound especially well heard at the left lower border of the sternum which may be explained by right ventricular dilatation when the left heart chambers are more constricted than the right or the right ventricular myocardium weak and atrophic Atrial fibrillation is common in the cases of chronic constrictive pericarditis (Pick s disease) and atrial flutter also may occur these arrhythmias were present in 20 (38 per cent) of 53 cases of chronic constrictive pericarditis (Paul Castleman and White 1948) The blood pressure and pulse pressure are low if the blood flow is much reduced by the hampering of the heart action

In a case with chronic constrictive pericarditis of long standing and attended by malnutrition the blood serum protein is often reduced to below 5 gm per cent and the albumin globulin ratio may be reversed favoring an increase in





FIG 140 Roentgenograms of thorax of G P age 45 with chronic constrictive pericarditis showing calcification of the pericardium (A) Anteroposterior view (B) right anterior oblique view

edema such a finding is due probably in part to the malnutrition in part to the loss of protein in the ascitic fluid and in part to the reduced liver function. There is usually but little anemia

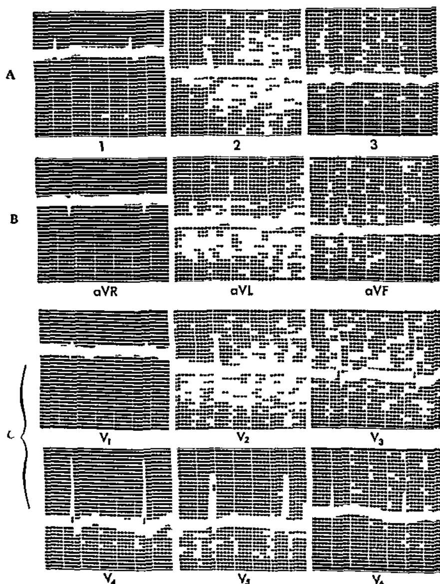


FIG 141 Electrocardiogram in chronic constrictive pericarditis male age 50 (*A*) Bipolar limb leads 1 2 and 3 (*B*) unipolar limb leads aVR aVL, and aVF (*C*) six precordial leads V to V inclusive Note especially the low voltage of the *QRS* waves in all the limb leads and the very low or inverted *T* waves throughout Despite the regular ventricular rhythm the *P* waves are not made out. Time = 0 04 and 0 20 second amplitude 1 mm = 0 10 mv

One of the most interesting varieties of chronic constrictive pericarditis which leads to pulmonary hypertension and right ventricular enlargement, acting much like mitral stenosis consists of preponderant involvement (constriction) of the left heart chambers, especially the left atrioventricular groove cardiac catheterization helps to confirm the pulmonary hypertension (White et al 1948), a special surgical approach can correct this as noted on page 735

Course and prognosis In the less important types of chronic pericarditis there is usually no interference with the normal duration and activity of life except as complications like valvular disease may affect the prognosis In many cases the pericardial adhesions are discovered only at postmortem examination in patients who have never had any cardiac symptoms or signs and have died a noncardiac death Even the original acute pericardial illness may be unsuspected or untraced The more marked cases however especially those with constrictive pericarditis generally develop symptoms and signs of heart failure or of systemic venous congestion with hepatic enlargement and ascites in youth With crippled lives they may survive for many years but finally usually in middle age they gradually fail and die from the effects of the pericarditis itself or from complications unless they are relieved by pericardial resection which affords much help or even cure in about half the cases

Complications The most frequent complications of chronic pericarditis have already been mentioned systemic venous congestion with hepatic enlargement and ascites and chronic valvular disease (in about half the cases) Hypertension coronary disease and bacterial endocarditis are infrequently associated with pericardial adhesions Atrial fibrillation is found occasionally Pleural adhesions are commonly associated with adhesive pericarditis the result of a mutual polyserositis in the past there may be chronic constrictive pleuritis as well as chronic constrictive pericarditis (Burwell and Ayer 1941)

Treatment There is no need of any particular treatment in most cases of adherent pericardium even if the condition is recognized but there are two important surgical procedures both called cardiolysis (καρδια heart and λυειν to free) which are indicated in certain cases These are (1) rib removal (thoracolysis) when there are extensive adhesions to the chest wall and (2) pericardial resection or cutting away of pericardium when there is compression of heart or great veins

Rib removal The simpler chest wall operation called Brauer s operation (Brauer, 1902) consists of the removal of several ribs and costal cartilages (usually three) on the left side over the precordium for a distance of about 10 to 15 cm from the sternum It quite probably can relieve the heart which is adherent to the chest wall of some at least of its extra work This operation has also been suggested and done in rare cases of marked cardiac enlargement without pericardial adhesions to relieve the heart of the task of displacing the anterior chest wall forward at each systole although it has not been generally adopted several patients have apparently experienced some subjective relief that is relief from the discomfort of the forceful heart action The operation

has been performed but little for adhesive pericarditis and now has for that purpose been largely abandoned since the Delorme operation of pericardial resection has widely and justifiably supplanted it indeed in former days before the diagnosis of crippling chronic pericarditis was made with any degree of accuracy the Brauer operation was done in some cases that proved to have marked cardiac enlargement with no pericarditis at all

As a matter of fact freeing the heart from extensive adhesions to chest wall or diaphragm would be much better carried out in these modern days of enlightened thoracic surgery by splitting the sternum medially lengthwise without permanent deformity of the chest such as follows Brauer s operation

Brauer L Ueber chronische adhasive Mediastino Perikarditis und deren Behand lung *Munch med W chnschr* 1902 XLIX 1072

Die Erfolge der Kardiolysis *Ibid* p 1732

Two discussions of cardiolysis for adhesive pericarditis took place at the Natur *historischmedizinischer Verein in Heidelberg May 13th and July 18th 1902 The* official report of the first of these two sessions is as follows (the translation is by myself)

'The speaker [Brauer] demonstrated two cases of chronic adhesive mediastino pericarditis and described in relation to these cases the etiology and diagnosis along with the expected further course and the pathologic structural changes doubtless present

Both patients showed in the most striking manner a systolic retraction of the lower anterior chest wall alternating with a vigorous diastolic rebound A collapse of the cervical veins was also evident during cardiac diastole The diastolic re bound of the chest wall was accompanied by a ringing tone which masked the usual second heart sound Kussmaul s signs of the pulsus paradoxus and of inspiratory dilatation of the neck veins were absent

In both cases there were signs of myocardial disease with enlargement of the liver and evidence of massive circulatory stasis

Since a significant increase of the work of the heart was caused by the systolic pulling in of the chest wall which rebounded immediately in diastole with so much force the speaker decided to free the heart by making a break in the bony ring of the thorax by the resection of ribs Through this procedure the heart would contract with the pulling in no longer of the elastic ribs but simply of a covering of the soft parts of the chest wall

Professor Petersen had happily brought about this result in one of these two patients by resecting the ribs covering the heart

'The consequence of this operation described above and carried out on the first day of April 1902 was very satisfactory The patient is both subjectively and objectively much improved Similar treatment in the case of the second patient will therefore be considered

At the second session in July the following report was made

Following his intention at the assembly of the 13th of May 1902 (this journal No 25) the speaker [Brauer] demonstrated the second of the two patients shown previously

Dr Simon had performed the operation on this patient which the speaker

had recommended This time a considerable part of the sternum was resected with the ribs

The expected result followed The patient whose heart no longer was obliged to pull in the entire anterior bony chest wall with each contraction but only a yielding surface improved appreciably found that he could move more freely with less dyspnea and was almost completely rid of signs of cardiac insufficiency which had been threatening him

Brauer L Die Kardiolysis und ihre Indikationen *Arch f klin Chir* 1903 LXXI 258

(Translation by myself)

About a year ago I described under the name of cardiolysis a method for the surgical treatment of adhesive mediastinopericarditis

Today I hope to be able to demonstrate to you the expediency of the procedure through the progress of both the cases which were reported at that time In the meantime since the early reports a third case has been operated upon and new observations have been made on the differential diagnosis and the determination of those cases which qualify for the operation

Moreover since one of the patients died a year after the operation from the accidental complication of an influenzal pneumonia the opportunity has been afforded to orientate the characteristics of the disease picture with the actual anatomical preparation and to discuss the different possible operative procedures

The most important indication for cardiolysis is afforded by those forms of adhesive pericarditis which cause a systolic retraction of a broad area of the thorax So long as vigorous thoracic movements of this sort are demonstrable a good result may be expected

Finally with what aim should one operate? Is it necessary actually to free the adhesions or sufficient merely to restore freedom of action for the heart by simply resecting ribs or sternum? The former procedure has been recommended by Delorme and by Beck [New York] but apparently it has not yet been accomplished It appears to be a very extensive procedure and it may be questionable whether or not one should subject the patient to it at all All this must first be ascertained through further cooperative work of surgeons and internists

The apparent operative success reported by Brauer may have actually been due in part at least to the breaking of a constricting cuirass around the heart *in the course of freeing that organ from the chest wall* even though there was no specific decortication

Pericardial resection The other operation mentioned above by Brauer more truly a freeing of the heart or cardiolysis consists of precordial rib removal with resection of the left side of the sternum whereby the pericardium and heart are exposed followed by the actual cutting away of as much of the thick constricting pericardium from the heart surface as is possible at the time with the resection also of any constricting bands about the great vessels, especially such as may involve the inferior vena cava under the sternum (Delorme 1898) An expert and experienced surgeon must be selected to undertake this difficult operation and anesthesia must be carefully admin

istered The operation is better postponed if possible until after the acute stage of any tuberculous pericarditis The younger and fitter the patient the less is the risk and the more likely is marked improvement to follow

Delorme Professor Sur un traitement chirurgical de la symphyse cardiopericardique *Bull et mem d l Soc d chir d Paris* 1898 XXIV 918

(Translation by myself)

If the surgeon feels legitimate regrets in publishing a method of treatment which he has conceived but been unable as yet to apply on the other hand he risks the loss of the advantage of the original idea and the compromise of its application if he waits too long It is to avoid this last difficulty that I have resolved to speak to you of a surgical treatment of cardio-pericardial adhesions concerning which I deposited a confidential note in 1895 at the Academy of Medicine and the application of which I have been unable to effect despite repeated appeals to my colleagues of the medical services of the Val de Grace Hospital This treatment consists of the resection or destruction of the cardio pericardial adhesions

Already a considerable number of striking cases of relief and cure following pericardial resection have been reported as in the case of the child shown in Figure 139 page 729 (Rehn 1920 Sauerbruch 1925 Churchill and White 1929 1930 White 1935 1942 with Harrison and 1948 with Alexander and Sweet and with Paul and Castleman Blalock and Burwell 1935 1941 Beck 1931 and 1943) Of our own series of 53 cases 42 were subjected to this operation 25 (60 per cent) were cured or much improved 16 patients died 6 as the result of the operation itself 5 from complicating diseases 4 from the pericarditis itself and one of unknown cause 7 of the 11 cases not operated upon were too ill for surgery and 2 others did not need it (Paul Castleman and White 1948) One of our cured cases is illustrated in Figure 139 page 729) In September 1950 Dr C S Beck of Cleveland kindly wrote to me of the results of pericardial resection in his series of 61 patients 38 patients (62 per cent of the entire group) were classified as clinically cured Ten others were somewhat improved and two cases showed no improvement One patient died on the table and ten others during the postoperative period or later

The further development of the surgical treatment of serious chronic pericarditis is a promising field for the future An important step forward has consisted of a new surgical technic consisting of a lateral thoracic approach allowing exposure of both back and front of the heart or better still of the splitting of the sternum which allows the chest to be widely opened with less later mutilation of the chest By either of these approaches important degrees of constriction of the left heart chambers can be cleared by posterior pericardial resection done prior to that over the anterior heart chambers such an approach is indicated when there is evidence of pulmonary hypertension as presented on page 732

Medical treatment of chronic pericarditis is obviously less hopeful although it may aid considerably in combating the complications especially the venous congestion due to chronic constrictive pericarditis The treatment of congestive heart failure in cases of serious heart disease especially with valvular deformities complicated by chronic pericarditis with or without important external adhesions is discussed in Chapter 30 The medical treatment of venous congestion in chronic constrictive pericarditis may be briefly summarized as follows limited activity with much rest diet low in salt limited to 1 gm or less of sodium daily, diuretic drugs by mouth and intravenously exactly as for congestive failure (see Chapter 30) and paracentesis of abdomen and thorax as needed When the blood serum protein is low a high protein diet is somewhat helpful Digitalis in chronic constrictive pericarditis is ineffective in controlling the congestion though it is very useful in controlling the heart rate when there exists the occasional complication of atrial fibrillation at one time as in 1937 when the second edition of this book was published it was thought by some including myself that a slow pulse in this disease might actually be harmful and that a relatively fast pulse should help to compensate so far as the blood flow is concerned for the small output of blood per beat but careful observation during the past decade has shown this not to be the case most of the patients being considerably better with slower pulse rates under digitalis therapy than with rates approaching or exceeding 100 per minute

Omentopexy (Talma operation) is contraindicated in chronic constrictive pericarditis since it in no way affects the fundamental condition

To prevent the development of pericardial adhesions in the course of acute pericarditis injections of air and oil into the pericardial sac have been suggested and made but such procedures have not yet been proved useful

Differential diagnosis When chronic pericarditis with external adhesions produces any signs at all it must be differentiated from cardiac enlargement per se from any cause with or without congestive failure This can be done in a few cases where the heart is clearly fixed in position and where other etiologic factors like hypertension and valvular disease are absent When other causes are combined with chronic adhesive pericarditis to produce cardiac enlargement and failure it is usually easy to diagnose the other causes and to miss the pericarditis Broadbent s sign may be misleading being found in some cases of marked cardiac enlargement especially of the right ventricle without adhesive pericarditis the retraction of the heart from the chest wall during systole simulating the tug of pericardial adhesions And as noted above chronic pericarditis even with calcification may be present without any cardiac enlargement or constriction at all

A previous history of acute pericarditis is naturally of great value in the diagnosis of pericardial adhesions

Chronic constrictive pericarditis causing enlargement of the liver with ascites (Pick s disease) must be differentiated from true cirrhosis of the liver This can usually be done easily there are two clearly distinguishing points

both to be found in the case of chronic constrictive pericarditis (1) engorgement of the neck veins and (2) abnormality of the electrocardiogram

It is also to be remembered that marked chronic mitral stenosis with or without tricuspid valve disease may itself be a cause of chronic hepatic congestion but in such a case the mitral diastolic murmur and other evidences of the mitral stenosis and tricuspid insufficiency are present

The usually insidious onset the liver engorgement with preponderant ascites (as compared with dependent edema) the increased systemic venous pressure (as shown by the neck veins) with relatively normal heart and the abnormality of the electrocardiogram are the clues which in combination make the diagnosis of chronic constrictive pericarditis certain

Finally chronic constrictive pericarditis is not polyserositis although it may follow it

C CONGENITAL PERICARDIAL DEFECTS

There are three types of pericardial abnormality of congenital origin all rare These are absence or defect of the parietal pericardium diverticulum or hernia and lack of attachment of the pericardium For a discussion of these and bibliography the reader is referred to Chapter 13

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PERICARDIAL SURGERY

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CHAPTER 28

VASCULAR DISEASE
DISEASES OF THE AORTA AND PULMONARY ARTERY
PULMONARY EMBOLISM
ANEURYSMS
DISEASES OF ARTERIES AND VEINS

Vascular disease like heart disease itself has seen a good many advances during the past seven years since the last edition of this book especially in the fields of diagnosis and surgical therapy but only the most important of these advances can find a place in this fourth edition

Blood vessel abnormalities make up an important part of the study of cardiovascular disease not only from the standpoint of the circulation as a whole but also from that of the heart itself Many vascular disturbances are of functional nature due to abnormal dilatation or constriction of arteries and capillaries and these will be discussed in Chapter 31 (Part IV Disorders of Cardiovascular Function) Structural vascular changes as they affect the heart and great vessels will be considered in the present chapter Diseases of the peripheral circulation per se however will be discussed but briefly in the present edition in order to save space in this expanding book which deals primarily with diseases of the heart and great vessels Many of the newer significant references to publications on peripheral vascular disease have however been added to the Bibliography and the reader is also referred to the newer textbooks on the subject

DISEASES OF THE AORTA

Organic disease of the aorta is exceedingly common but fortunately it is of little or no importance in the majority of cases Some change of the aortic wall is almost universal after the age of forty years

ACQUIRED AORTIC DISEASE

Etiology *Cause* There are four chief types of acquired aortic disease (1) atherosclerosis the most common type (2) dilatation due to hypertension or aortic regurgitation (3) infectious changes and (4) rarely traumatic lesions Besides these types there are occasional instances of aortic disease of unknown nature

The first and commonest lesion called atherosclerosis is found in considerable degree in old age but begins often in youth The cause of the abnormal deposition of cholesterol fat droplets and crystals in the intima of the aorta which constitutes atheroma is still unknown whether a fault in fat metabolism or of local tissue function or of other nature much study of these factors is needed to solve this very vital problem Heredity is the only recognizable factor that is fairly consistent it seems likely that several factors (especially heredity local strain and disturbed fat metabolism) may combine to cause atheroma

Dilatation of the aorta of moderate degree is a common result of chronic hypertension and of well marked aortic regurgitation and in rare cases is due in old age to a loss of elasticity with resultant senile ectasia (ἔκτασις a stretching out)

Infectious aortitis is frequently seen in youth and middle age most commonly and typically as a late manifestation of syphilis but it is also occasionally found as an acute lesion (called mycotic) in other infections such as rheumatic fever typhoid fever and tuberculosis Saccular aneurysms are almost invariably the result of syphilitic aortitis

Traumatic lesions the result of direct or indirect trauma (perforation blows strain) occur as a rule in the case of an aorta already diseased most commonly by syphilis atheroma or medial necrosis of unknown cause If the trauma is indirect it occurs usually at the time of the greatest distention of the aorta

Medial necrosis and hypertension combined with or without the additional element of trauma give rise in rare cases to a very important lesion consisting of a splitting of the aortic wall called a dissecting aneurysm

Age Naturally the great preponderance of aortic disease is found in older persons after the age of 45 years because hypertension and syphilitic aortitis are then more advanced and because atheroma is especially a senile change Atherosclerosis has however been noted frequently in otherwise healthy individuals between the ages of 30 and 50 years and sometimes even in children and youths On the other hand the aorta especially in the ascending portion is often astonishingly smooth and elastic in individuals over the age of 75 years in fact this appears to be the rule in persons who live to be very old it may be evidence of the inheritance of good arterial tissue Infectious aortitis is commonest in young and middle aged individuals syphilis being the chief factor between 40 and 50 years of age

Sex The male sex is more often the victim of aortic disease than is the female in the proportion of about 2 to 1

Pathology *Atheroma* (αθηρη crushed grain or porridge) begins as a deposition of cholesterol fat in the intima where it appears engulfed in lipoid

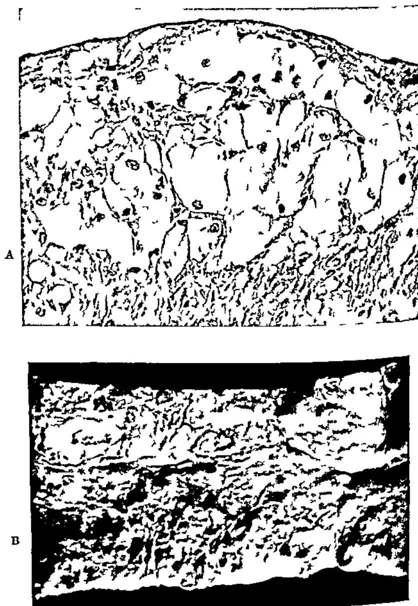


FIG 142 Photographs showing aortic atherosclerosis (*A*) Microphotograph showing atheromatous lesions of the aorta with cholesterol in the lipoid cells grossly the lesion was a pinhead sized orange yellow nodule (Kindness of Dr Timothy Leary) (*B*) Atherosclerosis of thoracic aorta showing well marked atheroma calcification and resulting ulceration (Jores *Arterien* Kindness of Julius Springer Berlin)

cells (Figure 142A) There are thus produced small fleck like areas which raise slightly the inner surface of the aorta encroaching a little on the lumen This encroachment in the case of the aorta is of little or no moment but in very small arteries it becomes important Gradually these areas tend to increase in size and number discoloring the aortic intima yellow At first the process is reversible the fat being taken up and away but finally there is a reaction of fibrosis in these areas in middle age or even in younger persons while in older individuals lime salts are deposited in them in either case stiffening re sults to which the term sclerosis (σκληρότης hardness) has been applied The development of the whole process from softening to hardening has been called atherosclerosis The aorta may eventually become more or less rigid and quite inelastic (Figure 142B) The atherosclerosis may then be a handicap though not a serious one to the circulation which is normally maintained in part by the elastic pressure of the aorta when it is filled with blood by ventricular systole The calcified areas or plaques may break or cause ulceration of the endarterium leading to intra aortic thrombus formation The descending aorta in thorax and abdomen is more often involved by the atherosclerotic process than is the ascending aorta—for unknown reason but perhaps because it is less adequately supplied with vasa vasorum Sometimes the descending aorta when it loses its elasticity becomes much elongated tortuous and even kinked (Roesler and White 1931) and has been known indeed to cause mild attacks of subacute intestinal obstruction (Palmer 1942) associated with the arteriosclerosis of the descending aorta especially the abdominal portion nonsyphilitic saccular aneurysms now and again occur It has al ready been noted that in very old persons the aorta especially the ascending portion may be extraordinarily normal resembling that of a young adult

Infectious aortitis is mainly of two types that in which the media or musculature is chiefly involved and that in which endarteritis is the primary lesion Rarely invasion of the aortic wall occurs directly by extension of infection through the adventitia from contiguous lesions as in the case of tuberculous lymphatic glands pressing against the aorta Slight infectious lesions may heal without causing any structural defect but there are six abnormalities of the aortic wall that more or less frequently follow aortitis especially of syphilitic origin These six defects are (1) weakening of the aortic wall with loss of elasticity and dilatation (2) aneurysmal pouches (3) rupture of wall either partial or complete (4) ulceration of the intima (5) thrombus formation on the inner surface of the aorta usually over ulcerated areas and (6) partial or complete obstruction of the mouths of aortic tribu taries—coronary innominate carotid subclavian and intercostal arteries The extensive infectious lesions in which a large percentage of the aortic wall is involved are almost invariably syphilitic in nature in such cases the ascending aorta is the chief site of the disease beginning a short distance (1 or 2 cm) above the aortic valve the media is the coat affected with destruction of muscle and elastic tissue patchy whitening of the aortic surface with wrinkling and secondary involvement of the intima (Figure 89 page 412 compare with

Figure 142B) The syphilitic lesion probably results mainly from occlusic of the vasa vasorum but treponemata themselves are found in the aortic wa Small localized aortic lesions are sometimes the early stage of syphilitic aortiti but often such lesions are due to other infection either directly involving th intima or through embolic invasion of the media by way of the vasa vasorur Occasionally these localized aortic lesions are complications of bacteri endocarditis and infrequently they are seen in rheumatic infections typho fever and tuberculosis There may result ulcerations small mycotic ane rysms and intra aortic thrombi resembling valvular vegetations which m contain bacteria

In the case of syphilitic aortitis the infectious process may also progre downward to invade the aortic valve and to produce a serious aortic regurgi tation (Figure 131 page 686)

Medial necrosis Small defects of the media of the aorta due to necrosis of unknown origin have become recognized as distinct from syphilitic or other well known infectious lesions (Erdheim 1929) they are apparently a factor in the production of dissecting aortic aneurysms

Saccular and dissecting aneurysms of the aorta will be discussed later in the present chapter

Rupture of the aorta is a common sequel of weakening of the wall and aneurysmal dilatation usually of syphilitic origin occasionally rupture results from dissection of the wall (dissecting aneurysm of the aorta) due to the combination of medial necrosis (of unknown cause) and hypertension or even without the hypertension it may occur as a complication of congenital coarctation of the aorta rarely rupture results from atheroma and in a few cases it is caused directly by trauma of a healthy aortic wall The perforation may be very small consisting of a minute devious tear through the dissected aortic wall or of a tiny point at the bottom of an aneurysm with slow or intermittent bleeding in very rare cases spontaneous healing may take place with or without recurrence later There may be a large linear tear often clean-cut as if with a knife especially when there is no previous aortic disease such a large tear results in a profuse rapidly fatal hemorrhage Bleeding from aortic rupture is usually internal into pericardial sac pleural cavity, mediastinum or other great vessels (pulmonary artery innominate artery superior vena cava innominate vein) infrequently it is external into esophagus trachea bronchus or through the skin when the aneurysm has perforated the bony chest wall

Spontaneous rupture of the diseased or weak aorta most often occurs du e unusual exertion but it may take place at rest commonest is the rupture of a saccular aneurysm almost always syphilitic next most common is complete or almost complete transverse rupture a little above the aortic valve then there are tears in the inner and outer coats not immediately opposite each other and finally there are the dissecting aneurysms (Harris 1938) Occasionally there are incomplete aortic wall tears that are an accidental findin autopsy (Perry 1942)

Simple diffuse dilatation of the aorta mainly of the ascending portion and arch common in chronic hypertension and aortic regurgitation is as a rule unimportant since the aortic wall may be otherwise normal with good muscle and elasticity if however there is in addition atherosclerosis medial necrosis or aortitis the hypertension or aortic regurgitation may be an important extra burden favoring the production of aneurysms and rupture Extreme ectasia is rare

Effect of aortic disease on the heart The heart itself may or may not show signs of involvement in the presence of disease of the aorta such involvement is either incidental due to coronary artery disease hypertension or valvular disease or it results from complications of the aortic disease such as syphilitic aortic regurgitation narrowing of the mouths of the coronary arteries or arteriovenous aneurysm by rupture of aorta into a great vein Left ventricular enlargement is the chief finding in such cases

Uncomplicated aortic disease does not cause any demonstrable change in the heart either functionally or pathologically

Symptoms There are no definite symptoms of aortic disease except those which result from the most common complications (1) distress due to pressure from aneurysmal dilatations (2) excruciating pain from tearing of the aortic wall in the case of dissecting aneurysms and (3) angina pectoris or pain elsewhere in the body caused by occlusion of the mouths of the coronary or other arterial branches Rare cases with slow bleeding from rupture may also have symptoms hemoptysis hematemesis weakness pallor Involvement of the wall itself without aneurysmal pressure medial dissection or arterial mouth occlusion has been blamed as a cause of symptoms especially of pain often of the nature of angina pectoris but there is no proof that simple aortic wall involvement can cause pain it is now quite certain that angina pectoris is a symptom of coronary insufficiency whether or not the result of narrowing or occlusion of the coronary mouths rather than that it is a symptom of aortic disease alone Usually there are no symptoms at all from disease of the aorta

Signs As in the case of symptoms so in the case of signs there is no evidence of slight structural disease of the aorta Extensive involvement often of syphilitic nature produces signs mostly dependent on dilatation of the aorta (Figure 143 over) Dilatation due to hypertension may also be visible by roentgen ray examination (Figure 96 page 476) Atherosclerosis if extensive results in an elongation and tortuosity of the aorta due to loss of elasticity this tortuosity with prominence of the aortic knob (uppermost curve of the arch to the left) evident by roentgen ray study is a very common finding in old age (Figure 144 page 749) Advanced atherosclerotic changes with calcification in the aortic wall make the roentgen ray shadow of the aorta more dense than normal

Roentgenology continues to be the most important means of detection of aortic disease for it is only when dilatation of the ascending aorta or arch has reached a high degree that it becomes evident on ordinary physical examination—inspection palpation percussion and auscultation As a matter of

fact even roentgenology itself is a crude method of diagnosis deformity or calcification of the aorta being necessary before the roentgen ray picture appears abnormal Frequently fluoroscopy shows greater dilatation of the aorta than is found at postmortem examination because of the dynamic dilatation present during life under high intra aortic pressure Marked aortic

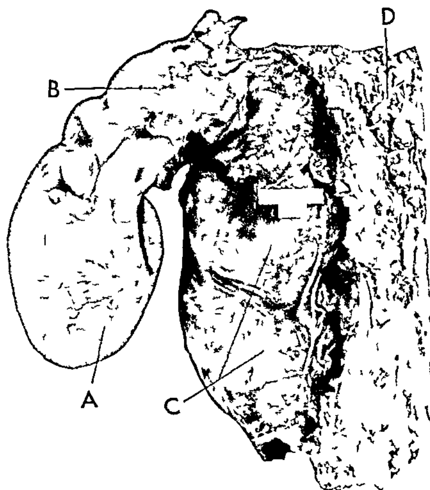


FIG 143 Syphilitic aorta with large aneurysm of the descending thoracic portion compressing and eroding the vertebrae and spinal cord with resulting paraplegia (*A*) Heart (*B*) arch of aorta (*C*) aneurysmal sac and (*D*) vertebral column (Kindness of Dr Pedro Castillo Havana Cuba)

pulsation is often visible fluoroscopically with marked aortic regurgitation especially when the heart action is very forceful Occasionally large or thick aortic plaques (calcification) are apparent on roentgen ray examination Finally it is important that roentgenologic examination should include the oblique views as well as the anteroposterior view because the shadow of the great vessels sometimes appears very wide in the anteroposterior view when

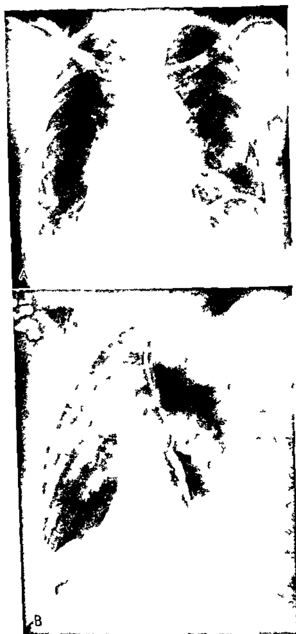


FIG 144 Roentgenograms showing a dense sclerotic aorta throughout its course in the thorax The heart is slightly displaced to the right by the high level of the diaphragm on the left The aortic notch in the barium filled esophagus is clearly visible at the beginning of the aortic arch (*A*) Anteroposterior view (*B*) left anterior oblique view

the aorta is simply kinked or tortuous and not dilated Erroneous diagnoses of dilatation and even of aneurysm have sometimes been made by hasty roentgen ray study In obscure cases roentgen films taken after the intra venous or more usefully still arterial or direct aortic injection of contrast fluid may give the necessary information

Dilatation of the aorta is usually accompanied by a systolic murmur more or less localized in the second intercostal space just to the right of the sternum varying in intensity and in extent of transmission but less intense and not so widely transmitted as is the systolic murmur of aortic stenosis The most important points of differentiation between aortic dilatation and aortic stenosis are the obvious aortic enlargement by roentgen ray study in the former and the palpable systolic thrill decrease or absence of the aortic second sound and decrease of pulse pressure often with plateau pulse in the latter Lesser grades of aortic stenosis are difficult or impossible to diagnose especially if there happens to be coincident aortic dilatation Dilatation of the aorta may be accompanied by signs of aortic regurgitation commonly organic and often due to syphilis but of functional nature in some cases marked rheumatic aortic regurgitation may result in aortic dilatation which is well shown by roentgen ray

Enlargement of the left ventricle as evidenced by physical examination roentgen ray study and electrocardiography (abnormal left axis deviation) follows aortic regurgitation complicating aortic disease while myocardial malnutrition scattered fibrosis and even infarction may follow narrowing of the coronary mouths producing the usual signs such as abnormalities of the electrocardiogram already described (Chapter 21) Heart failure of congestive type may succeed either of the two complications of disease of the aorta which especially affect the heart namely, aortic regurgitation and coronary mouth occlusion but especially the former Slight to moderate degrees of acquired aortic disease usually produce no signs of cardiac involvement

Signs due to aortic aneurysms will be discussed later in this chapter

Course and prognosis The course and prognosis of aortic disease depend on two conditions the etiologic factor and the degree of involvement Usually atherosclerosis is a slow process continuing to old age it is not in itself a serious condition except in very rare instances of aortic wall rupture or of intra aortic thrombosis over an eroding or brittle plaque Extensive atheroma is however an unfavorable omen for very long life since it exists more often in persons who die under the age of seventy five than in those who survive that age Infectious aortitis may not be serious but it often is acute or subacute bacterial endarteritis like acute or subacute bacterial endocarditis with which it may be associated is now curable by the administration of penicillin or other specific remedy in the course of weeks or months while syphilitic aortitis which used to limit life to an average duration of about three years after its discovery now permits a good many long survivors when the newer measures of treatment are carried out (see Chapter 16) In the severer cases of rheumatic infection and typhoid fever aortic lesions may develop

Rupture of the aorta as a rule is rapidly fatal but rare cases have existed in which the rupture was small or the bleeding gradual and even spontaneous repair has been noted

Aneurysms saccular or dissecting are serious the former permitting as a rule but a few months to a few years of life after their discovery and the latter generally fatal in the course of a few hours days or weeks infrequently a dissecting aneurysm allows survival for a few months or years with double aortic channel

Complications Important complications of disease of the aorta varying with the cause consist in the main of (1) cardiac enlargement and failure which may or may not be secondary to the aortic disease (2) aneurysmal formation and (3) rupture of the aortic wall The first and last of these complications have been discussed above aortic aneurysms will be discussed later in this chapter

Disturbance of the cardiac rhythm in aortic disease is unusual

Treatment *The treatment of aortic disease varies with its cause and degree* and with the type and extent of complications it is discussed separately under cardiovascular syphilis (Chapter 16) bacterial endocarditis (Chapter 15) congestive heart failure (Chapter 30) and aneurysm (the present chapter) There is no effective treatment as yet for atherosclerosis but avoidance of overexertion and overeating and protection against infection are advisable For a great many years potassium iodide has been given empirically in the treatment of arteriosclerosis there is a possibility but no real proof as yet, that this drug may have some influence in retarding the development of this process in man Choline and other lipotropic agents are now being tested in order to determine their therapeutic and prophylactic action in human atherosclerosis

Differential diagnosis The chief difficulty in the differential diagnosis of a diseased aorta comes in distinguishing it from a normal aorta since in a large majority of cases of atherosclerosis and inflammation there are no symptoms or signs and when there are such symptoms and signs they are often so slight or obscure that a clear diagnosis is impossible When aortic dilatation or other abnormalities are well marked they must be differentiated from mediastinal disease and tumors and from heart disease of other nature than that associated primarily with aortic disease Often the differentiation is difficult and in a large number of cases aortic disease is complicated by factors like hypertension coronary disease or valvular disease which obscure the primary aortic abnormalities

CONGENITAL AORTIC DEFECTS

Congenital aortic anomalies found mostly in young persons are due to maldevelopment in fetal life or at birth and include hypoplasia coarctation right aortic arch double aortic arch vascular rings involving aorta—especially double aortic arch and major branches of aorta (in particular the right sub

clavian) and transposition of the aorta and pulmonary artery septal defects between aorta and pulmonary artery, right ventricle or atrium, and patency of the ductus arteriosus these defects are discussed in Chapter 13

DISEASES OF THE PULMONARY ARTERY

The pulmonary artery is subject to nearly all the diseases and abnormalities that affect the aorta but in less frequency and degree Nevertheless cases exist in which this artery and its branches are involved to a considerable extent and it has been shown in recent years that structural changes in the smaller pulmonary vessels are extremely common and sometimes play a role in the precipitation or exaggeration of circulatory trouble (Costa 1927 Brenner 1935)

An important new method of studying the pulmonary circulation with particular reference to its blood pressure has been introduced in the last few years and has already clarified some hitherto unsolved problems this method consists in the catheterization of the pulmonary artery and its branches via the heart (see Chapter 10)

From a careful study of a series of 100 consecutive unselected autopsied cases at the Massachusetts General Hospital Brenner drew the following conclusions This lengthy survey seems to show that the pulmonary circulation plays an important part both in the physiology and in the pathology of the circulation as a whole but that this part is with rare exceptions passive rather than active The structure of the pulmonary vessels is such that they cannot be expected to play an important part in the regulation of the circulation through the lungs By far the most important influence in regulating the pulmonary circulation is the activity of the heart and particularly the state of balance between the two sides of the heart an increased output of the right side or a diminished output of the left causing congestion of the lungs and vice versa Again the pulmonary circulation has so great a reserve (provided by the ready distensibility of the small pulmonary vessels and the large number of reserve capillaries through which blood does not ordinarily flow) that it is difficult to embarrass it by occluding large branches of the pulmonary artery The cross sectioned area of the stem of the pulmonary artery must be diminished by 75 per cent before the systemic blood pressure falls and by 90 per cent before death occurs (in acute experiments)

Practically all the varieties of vascular disease occurring in the systemic circulation may be observed also in the pulmonary circulation Some forms such as syphilitic arteritis are less common and others such as septic and tuberculous arteritis are more common than in the systemic circulation Atherosclerosis is exceedingly common having been noted microscopically in some degree in 97 per cent of 100 consecutive unselected autopsies Its incidence is therefore as great though its degree is not so marked as in the systemic circulation Its very frequency makes it difficult to determine etiologic factors though its severity increases somewhat with age and with conditions

thought to be associated with a raised pulmonary arterial pressure such as cardiac disease or chronic pulmonary disease No constant relationship *is found between the thickness of the right ventricle and the degree of pul monary atherosclerosis*

Thrombi whether embolic or formed in situ are common in the pulmonary circulation being found in 28 of 100 consecutive unselected autopsies They ultimately become completely organized They rarely cause symptoms unless a large branch of the pulmonary artery is suddenly blocked

Etiology and pathology The commonest lesion of the pulmonary artery wall is *atherosclerosis* which is found particularly in cases of chronic mitral valve disease and chronic lung disease (especially extensive fibrosis) Such atheroma has been attributed to the increased strain on the artery and its branches by the hypertension in the pulmonary circulation In some cases pul monary atherosclerosis exists without any lesion elsewhere There is appar ently but little relationship between sclerotic changes in the aorta and in the pulmonary artery The pulmonary arterial atherosclerosis is usually slight consisting simply of yellowish fatty areas (atheroma) without calcification plaques which are so frequent in the aorta are unusual in the pulmonary artery Atherosclerosis of this artery is thus of little or no significance in most cases it is simply a pathologic finding of academic interest

Infection of the pulmonary artery is occasionally found in slight degree especially in rheumatic infection or bacterial endocarditis Syphilitic involve ment either of the main artery or of its smaller branches is very rare but it may be responsible for aneurysm or thrombosis of some part of the pulmonary arterial circulation

Endarteritis obliterans of the smaller pulmonary arteries which is a rare but serious and generally rapidly fatal condition has been attributed in some cases to syphilis but as a rule it is of unknown cause

Congenital defects include communications between pulmonary artery and aorta and transposition of these great vessels these have been discussed in Chapter 13 There is also hypoplasia associated at times with congenital pulmonary stenosis Congenital dilatation is occasionally seen with patency of the ductus arteriosus with interatrial septal defects and even with pul monary stenosis Aneurysmal dilatation due to weakness of the wall may also occur but much more rarely

Trauma is infrequent as a cause of pulmonary artery disease but rupture and traumatic aneurysm of the main trunk and of the branches have been noted as in gunshot wounds

One of the most serious of all affections of the pulmonary circulation is that of obstruction by *thrombosis* or *embolism* most commonly the latter Throm bosis is the result of a primary pulmonary artery lesion—endarteritis of in flammatory or obliterans nature—or perhaps of chronic stasis *except when* it occurs secondary to obstruction by embolism Embolism is a sudden in vasion of a generally normal pulmonary arterial tree by a clot from a throm bosed vein somewhere in the body (in the great majority of cases from legs

pelvis or abdomen)—this will be discussed in more detail in the next section of this chapter

Hypertrophy of the smaller pulmonary arteries with increased thickness of their walls is a common result of chronic pulmonary hypertension from any cause especially in younger patients

Finally *dilatation of the pulmonary artery* and its main branches without lesions of the wall except occasionally atheroma is a fairly common acquired finding with hypertension of the pulmonary circulation in mitral stenosis congenital atrial septal defects extensive blocking of the pulmonary circulation or advanced disease of the lungs Some of this dilatation is permanent but some is temporary due evidently to the dynamic effect of the increased blood pressure and acutely caused by massive pulmonary embolism before the circulation and the right ventricle fail Rarely pulmonary artery dilatation is congenital Regurgitation through the pulmonary valve may or may not be found in cases of pulmonary artery dilatation

The pathologic characteristics of the various lesions mentioned above are the same in nature but as a rule much less in degree than those described under aortic disease

Symptoms There are no symptoms of pulmonary artery disease itself except those associated with sudden occlusion of a large part of the pulmonary circulation by embolism with extensive obstruction of the smaller branches or with right heart failure In the case of massive pulmonary embolism there are at first usually air hunger and collapse and sometimes anterior chest oppression later fever cough hemoptysis and localized chest pain (due to infarction) usually develop if the patient survives the initial catastrophe With extensive obstruction of the smaller pulmonary vessels there are dyspnea and cyanosis When the right heart fails liver engorgement and dependent edema develop

Signs Signs of pulmonary artery disease are few In fact there are no signs at all unless there is dilatation of the main trunk and its major branches the presence of which may be shown by physical examination but much better by roentgen ray study or unless there is obstruction due to chronic endarteritis thrombosis or embolism when cyanosis and right heart failure may be marked The cyanosis due to the greatly limited area of pulmonary capillary surface exposed to the inspired air may be intense in rare cases especially in those with endarteritis to whom the term 'black cardiacs' has been applied Physical signs of pulmonary artery dilatation include a loud pulmonary systolic murmur accentuated pulmonary second sound increased percussion dullness at the left upper cardiac border and sometimes visible and palpable pulsation over the pulmonary artery A state of serious shock often fatal with very low arterial and venous blood pressures may supervene when there is sudden and considerable pulmonary obstruction due to embolism from peripheral venous thrombosis which occasionally occurs as a postoperative complication or even more commonly in the course of chronic heart disease

Frequently associated with abnormality of the pulmonary artery is right ventricular enlargement, revealed by various methods of study; there is left atrial enlargement only when the left ventricle has failed or mitral valve disease is present. With considerable dilatation of the pulmonary artery the valve ring may become incompetent and the murmur of pulmonary regurgitation may then be evident.

Signs of infection underlying lesions of the pulmonary artery are of course incidental and do not aid materially in the diagnosis except in determining the type, as in the case of syphilis or acute bacterial endocarditis.

Course and prognosis. The course and prognosis of pulmonary artery lesions vary greatly. Usually they are entirely favorable but in the case of extensive pulmonary endarteritis obliterans the structural defect itself may prove fatal in the course of a few months or years. In the case of chronic stasis of high degree in the pulmonary circulation thrombosis and infarction may be superimposed on serious heart disease as an insuperable burden, and in the case of pulmonary embolism death may result in a few minutes, hours or days, or recovery follow after a more or less stormy illness. As a rule pulmonary artery disease is a postmortem finding, not diagnosed or diagnosable during life.

Complications. Complications consist chiefly in enlargement and failure of the right ventricle. There may or may not be other cardiovascular lesions present. Heart disease, especially mitral stenosis and left ventricular failure, are common. Pulmonary arterial aneurysms and rupture are very rare.

Treatment. The treatment is that of the underlying disease or complication. In the case of obstruction due to endarteritis, thrombosis or embolism, oxygen therapy should be employed to reduce cyanosis and dyspnea. Operative removal of pulmonary emboli has been successfully accomplished (first successful case reported by Kirshner in 1924) and frequently advised in the past but only rarely has it been attempted, because it is excessively difficult to select the proper case and time for such a radical operation. It seems very unlikely from the experience of the last twenty years that such embolectomy will ever prove feasible. Preventive measures, however, have already proved their worth. If it is evident, for example, that pulmonary embolism has resulted from peripheral phlebothrombosis the leg veins should be ligated to prevent recurrence and for prophylaxis anticoagulant therapy is in order.

Differential diagnosis. The diagnosis of pulmonary artery disease is often impossible; only with well-marked changes is it more than a guess. Differentiation from pulmonary valve lesions may be very difficult; the presence of mitral stenosis, of chronic failure of the left ventricle, of chronic pulmonary fibrosis, of recent operation or accident (which would favor pulmonary embolism), and of pulmonary artery dilatation are the distinctive points which aid in the diagnosis of involvement of the pulmonary artery. Cardiac catheterization to determine the pulmonary arterial pressure is occasionally a helpful procedure. The differential diagnosis between pulmonary embolism and acute coronary occlusion is sometimes especially difficult, for that purpose serial

electrocardiography is of particular value (see Chapters 20 and 21 and the next section)

PULMONARY EMBOLISM

In the first two editions of this book pulmonary embolism one of the most important of all cardiovascular disorders was seriously neglected but this omission was largely corrected by the addition in the third edition of ten pages about this subject In the present edition references to new advances have been added

It is an astonishing and disconcerting fact that I and many others had been examining and treating patients for years without realizing what we know now namely that pulmonary embolism instead of being predominantly a surgical or rather postoperative complication is actually much more commonly a condition occurring in the practice of internal medicine particularly in heart disease itself Until recently it has been called all sorts of things uncommonly recognized during life for what it actually was It has not suddenly appeared out of the blue a new disease in its frequency we have merely at last become aware of it

Its great importance lies not so much in its frequency but rather in its serious significance and in its preventability It belongs in some detail in this book not only because it is a cardiovascular event of much importance but because like dissection of the aortic wall it involves the great vessels and is an intrathoracic disease that may simulate or complicate heart disease itself in contrast to the various peripheral vascular lesions and especially because in its protean manifestations and details it is not adequately presented in most of the medical literature even of the present day

Incidence Pulmonary embolism is variously recorded as being found in 8 to 12 per cent of routine autopsies in 5 to 10 per cent of postoperative deaths in 0 1 to 0 5 per cent of all cases operated upon and sooner or later in a large percentage of cardiac patients (31 per cent of autopsied cases of mitral stenosis and 48 per cent of autopsied cases of congestive heart failure—Levine and White 1937 and Kinsey and White 1940 respectively) In one autopsy series 60 per cent of the cases were medical (half of which were cardiac) and 40 per cent were surgical (Hampton and Castleman 1940) of another series of 247 cases 166 were medical 80 postoperative or posttraumatic and one occurred postpartum (Westdahl 1941) In a recent survey of cases at the Massachusetts General Hospital there were 273 cases (0 6 per cent) among 45 523 medical patients and 238 cases (0 24 per cent) among 98 642 surgical patients during the years 1936 to 1945 inclusive (Carlotti et al 1947) In my own cardiovascular practice the recognized incidence jumped from 0 4 per cent in the decade 1920 to 1930 up to 3 0 per cent in the decade 1930 to 1940 due in all probability to better acquaintance with the condition (White 1940) Even the pathologist and the roentgenologist with their accurate methods of study realize their large oversight of pulmonary em

bolism in the past (Hampton and Castleman 1940) After World War I the German medical writers commented on the increased postwar frequency of pulmonary embolism (Burwinkel 1928) which was variously attributed to poor physical condition and malnutrition to the increase of surgery and because of the advance of surgery to the subjection of more older persons to operations though these factors were quite possibly operative it seems likely that the recognition of the condition was also keener Erdheim the great pathologist of Vienna had been one of the few who was early cognizant of the true situation

Etiology *Cause* The one outstanding cause of pulmonary embolism is *phlebothrombosis of the leg veins* beginning as a rule in the calf and extending into the long saphenous and femoral veins in one or both legs The thrombus is usually bland and dependent on stasis in a local circulation that has already been defective either structurally or functionally it is not infective or based on infection and so the term phlebothrombosis is preferable to thrombophlebitis Other veins in the body pelvic abdominal brachial and thoracic are much less likely to be responsible even though they may be at or near the site of operation or injury that has occasioned the rest in bed Nor are the right heart chambers often the locus of origin of the clots special exceptions should be made in the case of bacterial endocarditis involving a congenitally deformed right heart chamber or valve or patent ductus arteriosus and myocardial infarction of the interventricular septum with resulting thrombus formation on the injured myocardium

The leg phlebothrombosis occurs with equal readiness in the medical and in the surgical or traumatic cases predisposed by the circulatory stasis occurring in chronic or acute illness as from heart disease with congestive failure myocardial infarction cancer abdominal and pelvic operations and serious accidents Excessive manipulation of the abdominal or pelvic viscera at the time of operation and a long sustained Trendelenburg position favor the leg vein stasis Sitting still for hours with the knees bent favors the occurrence of thrombosis in the leg veins in an older person

Exciting factors In the majority of cases the embolus breaks loose without any particular provocation but sometimes some strain is responsible especially administration of an enema or use of a bedpan

Age Pulmonary embolism occurs postoperatively much more commonly in older persons but is fairly frequent as a complication of heart failure in middle aged or young adults it is rare before the age of twenty

Sex The sexes are fairly evenly represented

Pathology The structural changes concerned with pulmonary embolism are three (1) the clot in the leg vein which becomes the embolus (2) the actual plugging of one or more of the pulmonary arteries by that clot and (3) the pulmonary infarct that may follow Each one has its signs and symptoms The first two conditions always occur but not the third

The clot itself is a very rapidly propagating thrombus loosely attached to the wall of the leg vein and often floating in the blood stream ready to break loose

at any moment If in the course of its evolution this clot becomes well fixed it then loses its threat and in time becomes organized in situ doubtless that frequently happens and we never know how often patients escape further trouble By the time a clot becomes solid and by obstructing a vein produces signs and symptoms that particular clot has lost its embolic tendency although a sister or daughter clot may still get loose Thus in phlebothrombosis the pulmonary embolus may come from the leg that seems normal the other leg being swollen and sore as the result of the venous obstruction which has revealed the underlying disease It is the lengthy clot from the long saphenous or femoral vein that is especially dangerous and that coiled up may massively block the main pulmonary artery

The actual *blockade of blood flow* in the pulmonary circulation varies tremendously in degree and location from almost complete obstruction of the main pulmonary artery to closure of a small branch on either side the former kills quickly the latter in an otherwise healthy person probably produces no symptoms or signs at all Rarely is the embolus a septic one or composed of tumor cells or in the dog made up of the long worms of Dirofilaria immitis The left lower lobe has been the most common location of embolism or infarction at the Massachusetts General Hospital but both lower lobes are frequently involved together during the years 1937 to 1943 the location of 171 pulmonary emboli at the Massachusetts General Hospital has been as follows left lower lobe 99 (57 9 per cent) right lower lobe 65 (38 0 per cent) right upper lobe 4 (2 3 per cent) right middle lobe 0 and left upper lobe 3 (1 8 per cent) Pulmonary embolism is often perhaps usually multiple sometimes as many as one to two dozen emboli enter the lungs in the course of a few days or weeks varying in size from small fragments of clot to thrombi a foot or more long which may cause rapid death

Pulmonary infarction is by no means a necessary sequel of pulmonary embolism being found in only about half of the recognized cases of pulmonary embolism The pulmonary circulation is so rich in anastomotic and collateral connections that infarction results only if the occlusion is large or the apex of one of the lobes is involved or some obstruction to the blood flow is already present as in congestive failure of the left ventricle or in mitral stenosis The infarction may be partial and temporary yielding no signs and leaving no scar or it may be complete with ample signs and scar formation Thus it is obviously important not to use the terms pulmonary embolism and pulmonary infarction synonymously

Symptoms The symptoms of pulmonary embolism vary from none to many, from mild to overwhelming The commonest is the sudden onset of *dyspnea* not attributable to effort or excitement or to abrupt heart failure from paroxysmal tachycardia in a cardiac patient Rarely an asthmatic type of breathing is set off A symptom that is a close second is *substernal oppressive pain* which often accompanies the dyspnea and in older patients with limited coronary reserve may include or actually consist entirely of angina pectoris due to the effect of anoxemia or of the strain of the event on coronary heart

disease already present on occasion the pain may predominate *A feeling of faintness* is common while a *state of shock* is not at all rare being found naturally in the more severe cases or in patients already quite ill before the pulmonary embolism occurs *Restlessness* and *sweating* are often seen as a part of the reaction to the embolism Other symptoms are uncommon nausea and vomiting cough chill and headache Sometimes a mere sense of uneasiness or malaise reveals the occurrence of a small embolus

Fever develops if there is an infarct in the lung but there may already be a slight febrile reaction to the underlying phlebothrombosis in the leg With a large infarct the temperature may rise to 103 or 104° F by mouth. Fever of a degree or two that occasionally accompanies congestive failure is more often due to pulmonary infarction than to any other cause it has been in the past wrongly ascribed to pulmonary infection which may to be sure occur (but less commonly) or to the congestive heart failure itself

Pleural pain on the affected side is a common complication if there is an infarct, becoming evident on respiration on the second day and continuing for a few days with or without a pleural friction rub

Blood spitting is important evidence in favor of the diagnosis if it occurs but it is actually relatively uncommon It is often in larger amounts than in the case of pneumonia and does not resemble the frothy pink sputum of the pulmonary edema of acute left ventricular failure Most cases of congestive heart failure do not raise any blood at all

Signs. The two most important signs of the acute process and for a while afterward are *cyanosis* and *tachycardia* out of all proportion to any evidence of heart failure pneumonia or fever The cyanosis is frequently of high degree and is the occasion for rushing oxygen to the patient. The tachycardia on occasion is of paroxysmal nature atrial ectopic or atrial fibrillation or atrial flutter and this abnormal rhythm may divert one s attention from the underlying lesion As a rule however the tachycardia often as fast as 140 to 160 is sinus in origin the patient may himself become aware of the fast pulse but usually he is more troubled by other things particularly the dyspnea and prostration

Jaundice is a rare but important sign of a large pulmonary infarct superimposed on a liver congested from heart failure and unable to cope with the excess of blood pigment.

Localizing signs either of the *phlebothrombosis in the leg* (tenderness swelling pain on flexion of the foot—Homan s sign) or of the *involvement of the lung* (local rales bronchial breathing pleural friction rub or fluid) are often conspicuous by their absence They should be looked for daily when found they aid greatly in the diagnosis

Laboratory data Information derived from laboratory study is usually less important than the symptoms and signs already presented sometimes it is helpful in confirming or even pointing to the correct diagnosis but at other times it is misleading because it shows so little or because it reveals unexpected findings

Roentgen ray examination At the onset and for 24 hours or more afterward there may be little to find wrong in the thorax by roentgen ray even with developing infarction of the lung except for elevation of the diaphragm on the affected side or distended main pulmonary trunks with decreased caliber of vessels below helpful signs which should be looked for If there is no infarction roentgen ray evidence may be lacking but sizable infarcts finally appear in the picture as shadows of any shape and size at the periphery of either lung often tucked away in the sharp costophrenic angles where they may be mistaken for fluid Besides the two difficulties with roentgen ray diagnosis of pulmonary embolism already mentioned namely the slow development of the evidence when such finally appears and its complete absence when there are no infarcts there is one other problem that is often insuperable namely that the shadow of an infarct may be hidden by the hydrothorax or pulmonary congestion due to underlying heart failure by pleural fluid resulting from the infarct itself or by the heart shadow which is so often enlarged in these cases.

Multiple shadows may appear in the lungs on the roentgen ray films due to recurrent emboli with infarcts and be mistaken for areas of bronchopneumonia or tumors (Figure 145A) and in recent years linear scars of pulmonary infarcts have been identified by pathologist and roentgenologist (Hampton and Castleman 1940) so that it is possible on occasion to unravel past episodes of pulmonary embolism (Figure 145B) Indeed sometimes old scars and fresh infarcts are present in the same case

In pulmonary embolism it is even more important to investigate the venous circulation in the leg than it is to study the lungs inasmuch as the threat to further trouble which may be fatal lies in the femoral veins Physical examination may quickly reveal the thrombosis by the discovery of tenderness, swelling or recently discolored skin and then roentgen rays are unnecessary but often (in over 50 per cent of the cases) there are no signs of the thrombosis One may of course assume that it exists none the less and go ahead with the ligation of the leg veins on both sides without more ado Some years ago it was the custom in various clinics for roentgenologic diagnostic purposes to inject some contrast medium (e g Diodrast) into the veins of the lower leg when thrombosis therein was suspected but this procedure has been in large part abandoned for two reasons (1) the veins even though not thrombosed were not always adequately filled and (2) on occasion thrombosis was actually precipitated or aggravated by the material injected

Electrocardiography In the majority of cases of pulmonary embolism the electrocardiogram is of no assistance A few cases about 10 per cent with severe enough pulmonary arterial obstruction to cause the acute cor pulmonale but without severe shock have electrocardiograms with characteristic pattern of dilatation of the right ventricle consisting of prominence of *S* waves in Lead 1 and in the precordial leads over the left ventricle of *Q* waves in Lead 3 low to slightly inverted *T* waves in Lead 2 inverted *T* waves in Lead 3 and in the precordial leads over the right ventricle (Leads V_1 V_2 and sometimes V_4) (McGinn and White 1935 Murnaghan McGinn and White 1943) (See Figure 99 and Chapter 20)



FIG 145 Roentgenograms showing (*A*) fresh pulmonary infarcts of lower lobe of right lung (kindness of Dr Richard Schatzki Mt Auburn Hospital Cambridge) and (*B*) clearing infarct upper portion of right lower lobe (kindness of Dr M C Sosman Peter Bent Brigham Hospital Boston) (*C*) (*a*) 12 days before and (*b*) one day after the occurrence of postoperative pulmonary embolism Note in *b* the thrombosed pulmonary arteries consisting of rounded shadows at the hilus regions in contrast to *a* and the decreased vascular markings below the hilus shadow on the right resulting from the decreased blood flow there

Besides the relatively small number of cases of pulmonary embolism showing the acute cor pulmonale pattern of electrocardiogram there are three other groups the largest of which because either of the small size of the embolus or at least of its failure to disturb the heart appreciably shows no change in the record from the normal or abnormal findings prior to the embolism Another fair sized group consisting of older persons with limited coronary reserve and often already afflicted by coronary heart disease may develop under the strain of the pulmonary embolism itself or of the vascular shock that accompanies it sufficient myocardial ischemia and anoxemia to produce coronary types of electrocardiograms (see Chapter 21), or indeed even acute myocardial infarction itself (posterior or anterior) without actual acute coronary thrombosis Finally severe depression of the coronary circulation with anoxemia in high degrees of pulmonary artery obstruction or vascular shock may itself cause temporary changes in the electrocardiogram which may simulate coronary heart disease though none has been present previously or will result after recovery

Thus it is apparent that the electrocardiographic findings in pulmonary embolism can be entirely normal quite characteristic of one pattern or another or very complicated due to a combination of several effects (Murnaghan McGinn and White 1943)

Other data Other laboratory findings in pulmonary embolism are unimportant Leukocytosis of slight to moderate (rarely high) degree is found when there is pulmonary infarction which explains the blood picture as it does the fever in many cases of congestive heart failure Examination of blood sputum urine and chest fluid shows nothing of special interest

Course and prognosis Pulmonary embolism may kill quickly though not instantaneously but more often there is recovery Of one group of 70 fatal cases 6 died in less than ten minutes and 16 more within an hour of the remaining 48 cases 20 died within twelve hours 4 between twelve and twenty four hours and 24 lived for one to several days (de Takats 1940) Of the cases *that recover many have recurrent embolism* in de Takats series of 100 cases 39 per cent suffered a second attack 12 per cent had a third 5 per cent a fourth 3 per cent a fifth and 1 per cent a sixth Doubtless the embolism is often so slight that it escapes notice altogether

This common recurrence of pulmonary embolism is one of its chief diagnostic features setting it apart from the two conditions with which it is so often clinically confused namely, myocardial infarction and pneumonia which do not so rapidly recur daily or weekly Perhaps a patient does have acute coronary occlusion or pneumonia to start with but when some sort of acute trouble in the chest keeps repeating itself every few days one should not only think at once of pulmonary embolism but also suspect that even the first attack of all may have been that very condition

Pulmonary embolism may occur as early as the first day after operation or accident or it may not happen till after three months in a large ser s of cases (897) at the Mayo Clinic approximately one half occurred between the

seventh and fourteenth days one quarter during the first seven days and one quarter after the fourteenth day (Barker et al 1941) The intervals between first and second episodes or between first and last (if more than two) in 207 cases of recurrent embolism in the Mayo Clinic Series was less than a day in 27 per cent between 1 and 7 days in 38 per cent more and less than 10 days in about four fifths of the cases In recurrent embolism the attacks vary greatly in severity from very mild to fatal thus the symptoms and signs will vary accordingly If the first attack or two have been severe however a succeeding slight attack may be enough to kill the patient or at least to cause symptoms and signs out of all proportion to the actual size of the embolus Likewise if serious heart or other disease is already present the very first pulmonary embolus even though small may precipitate congestive failure or myocardial infarction or be the cause of death in fact the commonest last straw which terminates life in patients with heart disease is pulmonary embolism

The mortality from recognized pulmonary embolism is variously estimated as 20 to 40 per cent but doubtless this figure is too high small emboli remaining undiagnosed Nevertheless it remains one of the most fatal of diseases

Recovered cases of pulmonary embolism may show no sequelae whatsoever or they may bear the linear scars of the pulmonary infarcts identified by roentgen ray and autopsy Such scars are as a rule entirely unimportant Rare cases however of massive pulmonary embolism recover to develop slowly the chronic cor pulmonale (doubtless having suffered originally from the acute cor pulmonale) The large clot in the pulmonary artery or its main branches becomes organized and the marked pulmonary hypertension gradually enlarges the right ventricle so that in the course of a few months or years death may come with right heart failure with or without recurrent pulmonary embolism from recurrent phlebothrombosis or pulmonary thrombosis in situ superimposed on the old organized embolus

Complications The commonest complication of pulmonary embolism is pulmonary infarction already described Attending such infarction there may be pleuritis and pleural effusion or a secondary infection of bronchopneumonia Acute vascular shock is an occasional and very serious complication Another reaction which has been described is that of bronchial and perhaps coronary spasm secondary to the vagal reflex set off by the event the frequency degree and importance of this have not been demonstrated In a minority of cases probably about 10 per cent there is an important degree of dilatation of the right ventricle (the acute cor pulmonale—see Chapter 20) In the presence of heart disease the serious complications of congestive heart failure and myocardial infarction may be further complicated by pulmonary embolism which vice versa, in its turn may precipitate either congestive failure or myocardial infarction

Treatment The lesser degrees of pulmonary embolism may require no treatment per se but cases of severe grade with dyspnea oppressive pain cyanosis and tachycardia with or without the acute cor pulmonale or shock need emer

gency treatment consisting of opiate (e g , morphine sulphate ¼ gr [0 015 gm] subcutaneously), oxygen (by tent or Boothby mask in high concentration preferably 100 per cent) and expert nursing care The first few hours are the critical ones

Other therapy is less important but may be helpful Atropine sulphate 1/100 to 1/60 gr (0 0006 to 0 001 gm) and also papaverine hydrochloride ½ gr (0 03 gm) have been advised subcutaneously or even intravenously for rapid effect in the syncopal type of pulmonary embolism as antispasmodics but their routine general value has not been proved Also digitalis solution (equivalent to 0 3 gm or 4½ gr of the international standard strength) or strophanthin (1/120 gr or ½ mg) has been advised to be given intravenously for the acute cor pulmonale but the effectiveness of these drugs also remains to be demonstrated

Otherwise only symptomatic treatment is indicated except for two important measures If the diagnosis is clear either the leg veins should be ligated at once or the anticoagulant heparin be given by vein or Dicumarol begun by mouth to maintain a clotting time of ½ to 1 hour The leg veins should be investigated the offending veins (commonly the superficial femorals) being ligated preferably on both sides to prevent further embolism which might well be fatal At the time of ligation it may be possible to remove the thrombus from the vein by suction Anticoagulant therapy alone may not be adequate in the face of thrombi already formed if pulmonary embolism occurs or recurs during its use vein ligation should be done at once Even this ligation however may not be a panacea although it is usually effective patients have been observed in whom a dangerous thrombosis above the site of the ligatures has followed the operation In rare cases it has been found necessary to ligate the inferior vena cava

Pulmonary embolectomy first carried out nearly two decades ago (1924) has not proved to be feasible at least as a routine measure Although it may conceivably be actually lifesaving in rare cases it is a radical procedure which may readily tip the delicate balance of the scales the wrong way it is not a simple operation in itself, it may not reach the offending emboli which may be out of reach in both lungs and in the majority of cases of pulmonary embolism recovery occurs without it

Prevention of the leg phlebothrombosis that gives rise to pulmonary embolism is more important than its treatment In the first place a state of physical and especially circulatory fitness should be established and maintained so far as possible especially prior to surgical operation At the time of operation as little is possible should be done especially in older persons and positions on the operating table conducive to blocking of the pelvic and leg veins should be avoided so far as possible Postoperatively and in any prolonged illness as from heart failure the leg circulation should be fostered by massage passive and active exercise and getting the patient out of bed at the earliest possible moment The routine postoperative use of the anticoagulants heparin and Dicumarol is open to question cases very prone to phlebothrombosis however should be so treated

Differential diagnosis The four conditions with which pulmonary embolism is most commonly confused are pneumonia congestive heart failure acute myocardial infarction and paroxysmal tachycardia The differentiation is usually easy by history and physical examination alone but now and again roentgen ray evidence or the acute cor pulmonale electrocardiogram or the course of the illness with recurrent attacks solves the problem The hardest cases are those in which two or even three of these conditions are superim posed in such patients careful detective work is necessary The most im portant clues pointing toward pulmonary embolism are leg phlebothrombosis recent operation or injury very abrupt onset unusual degree of cyanosis blood spitting of moment unusually fast pulse and respiratory rates in the presence of relatively slight fever and recurrence of attacks

COMMUNICATIONS BETWEEN THE AORTA AND THE PULMONARY ARTERY

There are four types of congenital communication between the aorta on the one hand and pulmonary artery right ventricle or right atrium on the other hand They are first and most common patency of the ductus arteri osus second rare cases of a persistent truncus arteriosus without separation into aorta and pulmonary artery third exceptional instances of communication between the aorta and pulmonary artery by arterial septal defect and fourth very rare cases of communication between aorta and right ventricle or right atrium by septal defects (see Chapter 13) In differential diagnosis a possible rupture of the aorta into right ventricle or right atrium in bacterial endocarditis and endarteritis has already been mentioned (see Chapter 15) and rupture of aortic aneurysm into pulmonary artery or heart chamber will be discussed below

ANEURYSMS

Vascular aneurysms (ανευρισμα a widening) are most commonly arterial infrequently arteriovenous Cardiac aneurysms so-called have been described in Chapter 25

SACCULAR ARTERIAL ANEURYSMS

Arterial aneurysms are not uncommon structural defects unimportant when small or involving a peripheral artery but often serious always a potential source of trouble through rupture and even subject to infection (bacterial endarteritis) Their incidence varies widely since it depends in large part on the incidence of syphilis and trauma in any community and doubtless also on their early recognition and satisfactory treatment Although partly because of earlier recognition and more satisfactory treatment of these conditions in the last two decades it is mostly because of prevention that aneurysms are defi nitely less common in some places than they were a generation or two ago

In a series of 600 postmortem examinations at the Massachusetts General Hospital in the years 1896 to 1900 there were six individuals (1 per cent)

who had syphilitic aneurysms four of the aorta and two of the innominate artery while in three more recent series of 600 autopsies each at the same institution in the years 1926 to 1930 1936 to 1938 and in 1950 there were three cases (0 5 per cent), two cases (0 3 per cent) and one case (0 16 per cent) respectively with syphilitic aneurysms five of the aorta and one of the innominate artery Mycotic and dissecting arteriosclerotic aneurysms are not included in these figures Altogether there were 54 aortic and 3 innominate syphilitic aneurysms in the first 5 600 autopsies at the Massachusetts General Hospital in a period of 33 years (just prior to 1930) There were in this same series 10 dissecting aneurysms of the aorta and a few mycotic aneurysms figures of which it is difficult to be certain about since they have been carefully looked for only in recent years

The diagnosis of syphilitic aneurysms was made clinically at the Massachusetts General Hospital in 113 of 51 875 patients (0 2 per cent) during the decade from 1900 to 1910 and in only 61 of 75 184 cases (0 08 per cent) during the decade from 1925 to 1935 despite the improved roentgenologic facilities for diagnosis These percentages show a marked reduction in recent years and are probably significant of a decreasing incidence of aortic syphilis in New England as evidenced also by a decreasing incidence of syphilitic aortic regurgitation

In a series of 12 000 postmortem examinations in Philadelphia 306 intracorporeal arterial aneurysms of all kinds were found in 268 patients (2 1 per cent) (Lucke and Rea 1921)

Etiology *Cause* Syphilis is the most common cause of arterial aneurysms of the aorta and other great vessels of the trunk about 90 per cent of such aneurysms being produced by this infection Arteriosclerosis has relatively recently become recognized as the next most frequent cause of aortic aneurysms especially in the abdomen though in the thorax arteriosclerotic aneurysms are rare (Ruffin Castleman and White 1941) Trauma is the commonest cause of arterial aneurysms in the extremities with the infections of bacterial endarteritis and rheumatic fever and congenital weakness of the arterial wall acting as infrequent factors

Age Because of the great preponderance of syphilis as a cause large arterial aneurysms are generally found in middle aged persons forty to fifty five years old However syphilitic aortic aneurysms may be found quite frequently in younger individuals also, especially in Negroes even before the age of thirty years and rarely in children with congenital syphilis Traumatic and non syphilitic infectious aneurysms may occur at any age but are most frequent in youth

Sex There is a great male preponderance in the incidence of aneurysm because of the far greater frequency in the male sex of the two chief causes syphilis and trauma The ratio of male to female incidence is about 10 to 1

Race Aneurysms are found 6 to 8 times more often in Negroes than in white people, not only because of the greater incidence of syphilis in Negroes

but probably also because of its less satisfactory treatment among them and particularly perhaps because of the heavy type of Negro labor

Pathology An arterial aneurysm consists of a marked dilatation of an artery local or general saccular or diffuse it ordinarily signifies a local bulging of the wall to form a sac The larger arteries are more often the site of aneurysms than are the smaller arteries because they are more often the seat of an infection which weakens the wall especially syphilitic mesaortitis and because they are under greater strain Of the larger arteries the aorta is most often involved and the ascending portion of the aorta more frequently than any other part because it is the usual location of syphilitic aortitis The relative frequency of aneurysms of various arteries was found to be as follows in two series of 530 cases (Crisp 1847) and 1 000 cases (Klotz 1926) respectively

Table 13

LOCATION OF ARTERIAL ANEURYSMS

	Crisp	*Klotz*
Thoracic aorta	175	610
Popliteal artery	137	
Femoral artery	66	
Abdominal aorta	59	108
Carotid artery	25	
Innominate artery	20	
Subclavian artery	23	
Axillary artery	18	
External iliac artery	9	
Cerebral artery	7	
Common iliac artery	2	
Posterior tibial artery	2	
Gluteal artery	2	
Pulmonary artery		
Brachial artery	1	
Subscapular artery	1	
Ophthalmic artery	1	
Temporal artery	1	
In the brain		133
In regions other than brain and aorta		[illegible]

In 23 of these cases there were aortic aneurysms in both thorax and abdomen

The relative frequency of sites of aortic aneurysms is about as follows on a basis of 10 for aneurysm of the ascending aorta ascending aorta 10 aortic arch 7 descending thoracic aorta 3 abdominal aorta 3 The chief sites of aneurysms other than in the aorta are the popliteal femoral carotid subclavian innominate axillary and iliac arteries and the chief sites of visceral aneurysms are the splenic and hepatic arteries

As noted above the chief cause of peripheral aneurysms in arms and legs is traumatic with bulging of the wall at the site of stab or gunshot wound or of crushing injury there having occurred a partial healing of the original lesion The chief cause of *cerebral aneurysms* is a congenital defect of the

wall of the circle of Willis at a junction of the vascular ring with one of the incoming branches in the course of years amounting to 30 or 40 or more the thin wall bulges at this point to form an aneurysm of about the size of a pea it is the rupture of this aneurysm in certain of the cases that gives rise to the important not very rare *subarachnoid hemorrhage* which abruptly indicates its presence by headache blood in the spinal fluid and sometimes syncope and death though recovery not infrequently occurs Although syphilitic mesaortitis (see Chapter 16) is the commonest cause by far of thoracic aortic aneurysms *arteriosclerosis* is a common cause of *abdominal aortic aneurysms* and may even account for an occasional thoracic aneurysm An interesting variant is the *senile ectasia of the ascending aorta* due to loss of elasticity and occasionally noted in old men or women without syphilis rarely does it reach the size of large syphilitic aneurysmal dilatation Ruffin Castleman and White (1941) analyzed 9 600 autopsy records of the Massachusetts General Hospital and found 60 syphilitic aneurysms of the thoracic aorta and only 3 syphilitic aneurysms of the abdominal aorta in contrast to 27 arteriosclerotic aneurysms of the abdominal aorta and only 3 arteriosclerotic aneurysms of the thoracic aorta in this same series there were 3 cases of well marked senile ectasia of the thoracic aorta On the other hand Scott (1944) reported that of 62 cases with aneurysms of the abdominal aorta 74 per cent were syphilitic 21 per cent arteriosclerotic and 5 per cent mycotic

A weakening of the arterial wall chiefly through the destruction or break of the muscular and elastic tissue causes a local or general stretching which in turn results in dilatation (Figure 143, page 748) If the process is gradual enormous outpocketings may occur so that saccular aortic aneurysms may develop of the size of the heart itself or even of a person s head Usually death from rupture heart failure angina pectoris or other complication takes place before an aneurysm can become very large especially if the process is rapid or the wall very weak The aneurysmal lining may be smooth or wrinkled atheromatous or ulcerated and the sac may be so filled with thrombus that it pulsates little or not at all Organization of the thrombus with little or no progression of the syphilitic process may follow a virtual repair of the aneurysm

A bacterial infection of the arterial wall usually a complication of subacute bacterial endocarditis, may result in a so called *mycotic aneurysm* When a lesion actually destroys the arterial coats it differs from the usual aneurysmal dilatation of an artery and so is then called a *false aneurysm*

Rupture of an aneurysm may occur anywhere an aortic aneurysm ruptures usually into the pericardial sac or a pleural cavity but sometimes into the mediastinum esophagus trachea great veins pulmonary artery, or atria and sometimes even externally through the skin

Dissecting aneurysms will be considered later in this chapter as a special type

The effect of aneurysms on the heart and other structures The heart itself is but little or not at all involved by an arterial aneurysm even by a large aortic

aneurysm unless aortic valve or coronary artery mouths are affected but secondary effects on various tissues or organs in the neighborhood of an aneurysm due to pressure are common such effects include erosion of sternum ribs and vertebrae obstruction and displacement of pulmonary artery esophagus and trachea collapse of a lobe of the lung and irritation or destruction of contiguous nerves causing pain or paralysis as in the case of pupillary and laryngeal abnormalities

Symptoms There are no symptoms of aneurysms themselves except as they cause pressure on surrounding structures (giving rise to dyspnea dysphagia cough hoarseness and pain) or affect the heart by their complications (giving rise to congestive failure or angina pectoris) It is of considerable interest to know that even large aneurysms may be symptomless the slow stretching and erosion of the arterial wall itself not ordinarily causing pain

Signs Signs of aneurysms are frequent but not always clear without complete examination the condition may remain undiscovered Signs are due in the first place to the vessel enlargement itself which may be seen or felt or if in the deeper part of the thorax observed by roentgen ray examination The anterior thoracic wall front of the neck popliteal spaces thighs and axillae are frequently the sites of the pulsating tumors caused by aneurysms bulging the skin and subcutaneous tissues out beyond their normal level Such aneurysmal swellings may be found even in the back at the left costal margin or in other unusual locations If an aneurysm is abdominal intracranial or deeply seated in the extremities it may be impalpable and invisible even to the roentgen ray No reliance can be placed on pulsation systolic murmurs and palpable systolic thrills over aneurysms they may or may not be present dependent on the depth of the aneurysm below the surface of the body the elasticity of the wall the size of the lumen and the presence or absence of thrombosis Aside from evidence of arterial enlargement itself there are frequent signs due to pressure on surrounding structures such as are produced by any tumor mass Arterial pulsation distal to an aneurysm is often delayed and decreased due not so much to the presence of the aneurysm as to a greater or lesser degree of occlusion of the arterial mouth which may lie in the aneurysm The radial pulses are frequently unequal in cases of aneurysm of the thoracic aorta and sometimes one pulse or rarely even both pulses may be absent adequate circulation being maintained in the arms by collateral blood supply Very rarely clubbing of the fingers may result from inadequacy of the circulation in one hand or in both hands due to the effect of an aortic aneurysm In aneurysms of the thoracic aorta the Wassermann reaction is usually positive it was found to be positive in 50 cases (82 per cent) among 61 Negroes with thoracic aortic aneurysms (Sanford 1931)

The most reliable evidence of aneurysms of the thoracic aorta is to be obtained by roentgen ray study especially of those involving the arch or descending aorta a pulsating bulge of the aorta itself is the roentgen ray evidence (Figure 146 page 770) Both the new electrokymography (see Chapter 8) and roentgen ray study of the contours of heart chambers and great vessels out

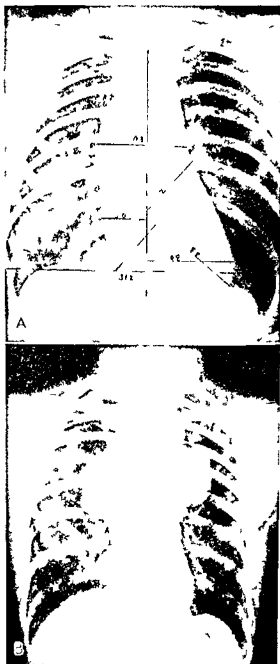


FIG 146 Roentgenograms showing aortic aneurysms (*A*) Small aneurysmal bulge of the ascending aorta due to syphilitic aortitis with poorly defined aortic knob and normal heart size (*B*) Multiple aneurysms of the thoracic aorta with normal heart size

lined by Diodrast injected into vein or artery can be very helpful in doubtful cases but careful technic and rich experience are usually needed to get the best results Electrocardiography is of no value in the diagnosis of aneurysms

On occasion in the absence of roentgen ray examination the very first evidence of an aortic aneurysm has been its rupture with fatal hematemesis for example

Course and prognosis A small traumatic aneurysm may not in any way limit activity or duration of life but a large aneurysm of a large artery especially since it is commonly syphilitic generally causes death in a few months to a few years and is associated with very serious disease The usual aortic aneurysm has an unfavorable prognosis but occasional cases are encountered in which such an aneurysm may remain more or less latent without change for 5 to 15 years with or without special treatment The most important point often overlooked concerning the prognosis and re ult of treatment of an aneurysm especially one of the thoracic aorta is that hard physical work has an unfavorable effect on the course of life The more strenuous the activity the shorter the life and the poorer the result of therapy

Rupture of an aortic aneurysm is not always fatal Small leaks may heal and even perforation into the pulmonary artery is compatible with months to a year or more of life (Porter 1941 White Chamberlain and Kelson 1941)

Complications The chief complications of aneurysms already mentioned are those due to secondary cardiac involvement pressure effects on surrounding structures and rupture

Treatment The treatment of aneurysms is of three kinds (1) that of the cause (2) that of the complications and (3) that of the aneurysm itself If syphilis is the cause (as it often is) and there is no heart failure specific therapy should be instituted with care as outlined in Chapter 16

In earlier editions of this book the reader was warned that the progress of this treatment must be followed in great detail and the heavy metals discontinued if symptoms of cardiac failure appear or if the aneurysm increases rapidly in size apparently as the result of the rapid resolution of the lesion by the drugs but the introduction of penicillin in the treatment of syphilitic aortitis renders much of this old advice now obsolete

Serious complications of heart failure and angina pectoris are to be treated as outlined in Chapters 21 and 30 of this book Pain due to pressure on and erosion of surrounding structures may be relieved temporarily by morphine but paravertebral alcohol injection or sympathectomy which affords more permanent relief is much to be preferred

In some cases where an aneurysm is saccular or easily accessible surgery may be indicated For a peripheral aneurysm obliteration of the sac has been done by rapid or gradual ligation of the artery in one or several operations The speed of arterial occlusion which may be extended over weeks or months depending on the extent of collateral circulation to the part of the body supplied by the artery involved A second procedure has been the wiring with or without electrolysis of saccular aneurysms of larger arteries like the aorta,

here a coil of platinum gold or silver wire is inserted into the aneurysmal sac preferably under roentgen ray control The presence of this wire and the passage through it of a small electric current may result in thrombosis in the aneurysmal sac tending to retard further progress of the lesion and to relieve distress such thrombosis however is by no means a constant result of this procedure The third surgical maneuver is to support the affected vessel or sac by surrounding it with strong connective tissue for example a sheet of fascia lata or with cellophane In August 1949, Abbott reported having applied cellophane to thoracic aneurysms in 32 instances with internal wiring in addition in four of these patients The majority of the lesions were syphilitic in origin On two occasions the procedure was carried out even in the presence of active massive hemoptysis All of these methods have been employed but the first is most often applicable and is the method of choice for peripheral aneurysms Care must be used to ascertain the presence of a sufficient collateral circulation before the artery in question is occluded The accompanying vein should be ligated with the artery

Differential diagnosis An arterial aneurysm is usually easy to diagnose except when it is deep-seated but when thrombosed it is sometimes very hard to differentiate from a tumor of other nature especially if that tumor is vascular and pulsating The close structural relationship to some artery the marked pulsation often present and the history of trauma or history or proof of syphilis are the most important findings favoring a diagnosis of aneurysm All methods of study must be used in doubtful cases especially in patients with thoracic and abdominal aneurysms

DISSECTING ANEURYSMS

Dissecting aneurysms must like arteriovenous aneurysms be considered by themselves for they form a distinct though small clinical and structural pathologic group (Shennan 1934) They involve chiefly the aorta occasionally the first part of the aortic branches due to extension from the aorta and rarely other vessels such as the coronary arteries independently

Until the last decade dissecting aortic aneurysms were merely postmortem surprises but now they are frequently recognized clinically as evidenced by the steady accumulation of reports of correct antemortem diagnoses

Etiology *Cause* The essential cause of dissecting aneurysms is a weakness in the media in the case of the aorta a medial necrosis of unknown cause (Erdheim 1929) A second factor usually of great importance is hypertension A third factor infrequently is atherosclerotic disease of the arterial wall. Syphilis is only very rarely a contributing cause apparently in only 2 of 64 cases reported by Mote and Carr in the year 1942 Strain or even trauma may be rarely a precipitating factor (Leonard 1945)

Age Dissecting aneurysms are found most commonly in middle aged and elderly subjects rarely before the age of 30 years A very young case of dis-

secting aneurysm of the aorta has been reported within the last few years in a boy 15 (McLaurin 1945)

Sex The male sex is predominantly affected in the ratio of about 3 to 1

Pathology The dissection apparently begins in the media as the result of the rupture of a vas vasorum but the intima quickly breaks through into the medial lesion by tearing sharply in a horizontal or oblique direction part way around the inner circumference of the aorta in its ascending portion or in the arch less commonly in its descending portion in thorax or abdomen (Figure 147 page 774) Under a high head of pressure (most of the patients have hypertension) the intra aortic blood penetrates into the media as a rule splits it extensively up and down but sometimes only up or down and occasionally dissects its entire length from aortic valve to bifurcation at the common iliac arteries The dissection occurs around ½ to ¾ of the circumference of the aorta and the blood in the medial split bulges the wall out in a variable but usually only moderate extent of ½ to 1 cm thickness Secondary tears through the intima are likely to be found at the upper and lower ends of the dissection even into one of the iliac arteries thus producing an extra channel through which the blood passes In most cases in the course of minutes hours or days the aorta ruptures completely as the result of a tear through the adventitia with sudden death due to extensive hemorrhage into pericardial or pleural cavity in a few cases the lesion heals sufficiently so that the extra aortic channel becomes lined with endothelium to give a double barreled aorta A constant and important complication is the involvement in the process of dissection of the mouths of the aortic branches with compression of these vessels and resulting effects of the sudden blocking of the local circulation as in the case of an iliac a coronary or an intercostal artery

Careful search of the aortic wall histologically at the site of rupture has revealed in most cases an area of unexplained degeneration or necrosis in the media

Symptoms In a few cases the arterial dissection may apparently be either symptomless or so obscure in its symptomatology that it cannot be diagnosed As a rule however there are two symptoms that are more or less characteristic and when added together almost pathognomonic Pain attending the splitting of the aortic wall is usually excruciating and extensive radiating from mid thorax front or back through the chest down the back and even into the thighs or up into the neck The pain in the thorax or back comes suddenly at its maximum and is often prostrating inducing a state of shock or even death If the patient survives the pain usually lasts for hours sometimes 24 to 48 hours requiring morphine repeatedly it may recur if there is an extension of the dissection

The other important symptom or group of symptoms is dependent on the blocking of the circulation to some important part or parts of the body especially legs viscera or brain Pain numbness coma and other symptoms may result. The very multiplicity of symptoms in some cases aids in the diagnosis

Signs There are no pathognomonic signs of dissecting aneurysms In the case of the aorta a systolic murmur at the base of the heart transmitted to neck and along the spine may be heard and an aortic diastolic murmur has been noted but these murmurs are far from constant Chronic hypertension and some cardiac enlargement therefrom are almost invariably present The

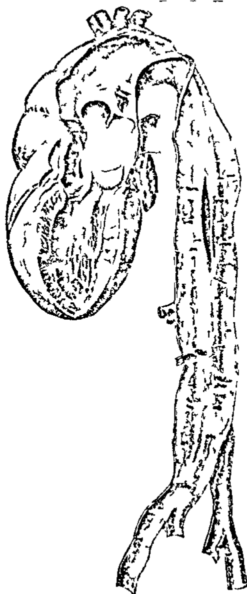


FIG 147 Drawing showing dissecting aneurysm of the aorta beginning in the ascending aorta and extending the entire length of the aorta into the common iliacs (W G MacCallum *A Text book of Pathology* 19_8 W B Saunders Company Philadelphia)

blood pressure often remains high after the dissection occurs or it may sink rapidly and to a low level temporarily during the state of vascular shock that commonly appears and may rise again with recovery Arterial pulse obliteration may be found due to compression of one of the aortic branches this is most commonly observed in the legs where other signs of vascular occlusion develop

Fever and leukocytosis of slight to moderate degree are common for a few days or of low grade even for a few weeks after the dissection of the aortic wall

Roentgen ray examination is rarely helpful unless a comparison of the shape and size of the aorta in a film taken before the acute illness can be accurately made with the aortic shape and size after the occurrence of the dissecting aneurysm slight changes in shape and caliber are to be expected Very rarely a larger bulge than usual of the dissected aortic wall may be noted by roentgen ray with calcified aortic intima visible well within this shadow

Electrocardiography is helpful because of its negative findings except in rare cases where one or the other or both coronary arteries may be involved in the process with more or less occlusion Usually the electrocardiogram shows no striking change from records taken prior to the acute illness such records may be expected to show in some cases the hypertensive pattern (see Chapter 19)

Course and prognosis Dissecting aneurysms of the aorta are usually fatal as the result of rupture through the adventitia in the course of minutes to days in three quarters to four fifths of the cases Death in such individuals occurs suddenly even though they may seem to be convalescing satisfactorily Certain cases survive a few months to a few years and may die noncardiovascular deaths in some of these the postmortem finding of a double barreled aorta has been a complete surprise Sudden death has been reported from spontaneous rupture and dissecting aneurysm of the left anterior descending coronary artery with compression and complete occlusion of the lumen (Helpern 1947)

Complications As noted above the chief complications of dissecting aneurysms are external fatal rupture and blocking of the circulation to some part of the body (especially legs heart and brain)

Treatment So far the only treatment for dissecting aneurysms is absolute rest for weeks probably six at least special nursing care at the onset of the acute illness *and symptomatic therapy by morphine for pain and shock and* for symptoms due to obstruction of various peripheral or visceral arteries No surgical therapy appears justified as yet

Differential diagnosis There are two conditions particularly with which dissecting aneurysm of the aorta is likely to be confused coronary thrombosis and peripheral embolism The intense thoracic pain followed frequently by a state of vascular shock with drop in blood pressure and later by fever and leukocytosis strongly suggests acute coronary occlusion but there are certain clues usually present which point to the correct diagnosis the sudden onset of the maximal pain instead of the building up of the pain in the course of a

few minutes as is the case with coronary occlusion pain the radiation of the pain usually to the back or its original presence there the radiation of the pain down the back often to the legs the evidence of rapid blocking of peripheral arteries before embolism from endocardial infarction is possible and the usual absence of characteristic coronary changes in the electrocardiogram Dissecting aortic aneurysm as a cause of blocking of the peripheral arteries can be distinguished from embolism by the initial occurrence of severe chest or back pain just prior to the arterial block (by only a few minutes) and the absence of any adequate explanation for intracardiac thrombosis where the embolus would have to originate

Pulmonary embolism, another thoracic emergency is less likely to be confused with dissecting aneurysm of the aorta because of the preponderant dyspnea cyanosis and tachycardia attending it with much less pain a frequent story of recent operation or injury the common occurrence of phlebothrombosis in the legs and the occasional bloodspitting and localized pulmonary signs

ARTERIOVENOUS ANEURYSMS

An important vascular lesion uncommon but of considerable interest is a direct communication between artery and vein this is called an arteriovenous aneurysm or fistula It does not include the small vessels which normally may join arterioles directly to venules without the interposition of capillaries that have been found in certain parts of the body as in the fingers (Grant and Bland 1931) and in the myocardium (Wearn et al 1933) Although an arteriovenous aneurysm may occur anywhere in the body and between vessels of any size it is most common in the extremities between arteries and veins of medium caliber like the popliteal vessels Usually trauma is the cause a perforating wound uniting an artery with a vein either directly or by rupture of traumatic aneurysm hematoma or infected area Such a fistula may result accidentally from surgical operation Much less often primary arterial disease namely infection ulceration or aneurysm is responsible as in the case of the rupture of an aneurysm of the ascending aorta into the superior vena cava A congenital arteriovenous aneurysm is not so rare as was once thought it is an infrequent but important anomaly of the pulmonary circulation resulting in cyanosis and cardiac enlargement

The short circuit of a considerable amount of blood produced by a large arteriovenous aneurysmal shunt has three chief effects In the first place the vein is widely dilated the dilatation extending generally far along the course of the vein distending the valves if present and rendering the vein incompetent There is seen and felt a marked arterial pulse in the vein and a blocking of venous blood flow occurs distal to the aneurysm The artery also takes part in the dilatation but to a much smaller degree In the second place a loud often roaring continuous murmur with systolic accentuation and a palpable continuous thrill is evident over an arteriovenous aneurysm of large or average size even when it is deep-seated These signs are the chief basis for the

diagnosis In the third place the lesion may be serious because of the effect on the heart the left ventricle becoming considerably enlarged except when the arteriovenous aneurysm is small The blood flow is much increased by an arteriovenous shunt of large size and it is this fact that is doubtless respon sible for the effect on the heart

An interesting lesion which like patency of the ductus arteriosus has an effect on the heart and circulation similar to that of an arteriovenous aneurysm or shunt is perforation of the aorta into the pulmonary artery—here the blood stream goes from the high pressure systemic circulation into the low pressure pulmonary circulation with deleterious effect death if the perforation is large heart failure if small

The course and prognosis are unfavorable with arteriovenous aneurysms of large size unless they can be treated heart failure developing in the course of a few months or years A communication between aorta and superior vena cava is especially serious death coming as a rule quickly in a few hours days or weeks Rupture of the arteriovenous aneurysm is an occasional complication

The treatment consists of ligation of the arteriovenous aneurysm about three months after the development of the lesion if traumatic (to allow the establishment of an adequate collateral circulation) if such ligation is possible Rapid relief usually follows ligation with decrease or disappearance of cardiac enlargement and prevention of heart failure A case of cure of Streptococcus viridans infection of an arteriovenous aneurysm by excision of the aneurysm was reported by Hamman and Rienhoff in 1935

PERIPHERAL VASCULAR DISEASE

Although peripheral vascular disease is often set off by itself as a special province and is per se widely spread throughout the entire body nevertheless it forms but a part of the larger realm of cardiovascular disease and has fre quent and intimate associations with diseases of the heart and great vessels

DISEASES OF ARTERIES

Some of the more intimate associations have already been referred to such as *periarteritis nodosa* which is in reality a systemic disease involving many parts of the body including the coronary arteries damage to which can seri ously affect the heart (see Chapters 21 and 23) Arterial obstruction by *thrombosis* superimposed on *sclerotic disease* or *endarteritis obliterans* (Buer ger s disease) can jeopardize the health and result in gangrene of the legs especially in men already laboring under the strain of some type of heart dis ease usually coronary or hypertensive or both and *arterial embolism* may be a serious complication and even precipitate death in patients with rheumatic heart disease subacute bacterial endocarditis and coronary heart disease (see Chapters 14 15 and 21) On the other hand *intermittent claudication* which consists of leg muscle ache especially in the calves on walking due to insuffi cient blood supply secondary to arterial obstruction may limit the activity of

a patient with coronary insufficiency to such degree that this more important disease is less of a hazard to life *Endarterectomy* recently introduced in France (Leriche 1946 Bazy 1948 Laubry and Reboul 1950) has been an effective new therapeutic measure helping certain cases of arterial obstruction much more than have vasodilating agents and sympathectomy although aminophylline has helped some cases (Kissin et al 1951)

Arterial spasm is an occasional disturbing accompaniment of venous thrombosis in the extremities or of arterial embolism and as a special entity produces the important condition of *Raynaud s disease* (Raynaud 1862) which giving rise at first to the syndrome of dead fingers (doigts morts) can progress to serious structural changes in the tissues and even to gangrene (see Chapter 31) There is still some question as to whether either arterial spasm or endarteritis obliterans of the Buerger type affects the coronary circulation

Arteriosclerosis of the media of the arteries of the limbs so often found in laborers and called *Monckeberg s sclerosis* (Monckeberg 1924), is an entirely different process from the atherosclerosis of coronary and cerebral arteries and aorta as a matter of fact I have very infrequently found tortuous calcified and beaded radial arteries in my patients with coronary heart disease whose radials are usually soft and similarly have infrequently noted coronary heart disease in cases with Monckeberg s peripheral arterial sclerosis

Aneurysms saccular due to syphilis mycotic involvement arteriosclerosis and trauma *dissecting* and *arteriovenous* all of which may have an important effect on heart and great vessels have been discussed in some detail earlier in this chapter

DISEASES OF VEINS

The most common diseases of the *veins* are *thrombosis* and *varicosities*. The former in its most important relationship of leg vein thrombosis has been discussed earlier in this chapter in the section on Pulmonary Embolism another important though rare abnormality is that of thrombosis of the great veins particularly the venae cavae an example of which is illustrated in Figure 148 Pressure by surrounding structures (e g tumors) trauma infection and stasis are causative factors if the superior vena cava is blocked the so-called superior mediastinal syndrome results and if the inferior vena cava is thrombosed high up there develops the inferior mediastinal syndrome Varicose veins are more of a nuisance than a serious disease but on occasion they may be associated with ulceration and infection and when very extensive may actually give rise to circulatory insufficiency due to the pooling of enough blood in huge varicose veins so that there is a serious reduction of the volume of blood returned to the heart with resulting faintness and dizziness (Chapman and Asmussen 1942) *Venous spasm* is an interesting phenomenon which may on occasion cause difficulty as in occasional instances of cardiac catheterization

Portal and splenic vein thrombosis can be very serious with obstruction and ascites resulting therefrom as also from hepatic cirrhosis which may require consideration of portocaval anastomosis via renal circulation or vena cava

directly One of the important complications of such diseases is dilatation of the esophageal varices that are so prone to bleed freely

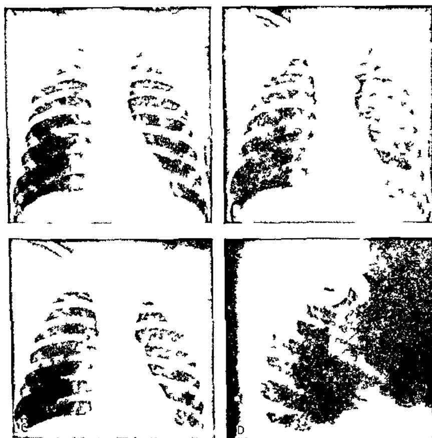


FIG 148 Roentgenograms of thorax showing visualization of great veins by Diodrast injection Case of young man with traumatic block of superior vena cava indicated clearly in (*B*) and not visualized in the control record (*A*) (*C*) Film taken shortly after (*B*) showing filling of vena azygos minor and a pericardial vein (*D*) Oblique view shows very well the large collateral vessel vena azygos minor taking blood from the upper superior vena cava down to the abdomen to empty into the inferior vena cava (With the kind help of Dr George P Robb 1 Madison Ave New York City)

For further discussion and details of the etiology diagnosis and treatment of peripheral vascular disease the reader is referred to the references to publications in the Bibliography at the end of this chapter

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PART IV

DISORDERS OF CARDIOVASCULAR FUNCTION

CHAPTER 29

THE CIRCULATION OF THE BLOOD IMPORTANCE OF DISORDERS OF CARDIOVASCULAR FUNCTION CLASSIFICATION OF TACHYCARDIA, BRADYCARDIA, AND ARRHYTHMIA

Although William Harvey announced his discovery of the circulation of the blood over three hundred and twenty years ago (1628) it has been only within recent times that the circulation as a whole has been properly understood The heart is but the central organ though it is to be sure the most important link in the chain Even the blood vessels vital though they be do not complete the picture It will be worthwhile for a moment to survey the various detailed parts of the body that share in the fascinating process of getting the blood to go where it should Let us start with the right atrium where at its junction with the superior vena cava lies the pacemaker the ultimum moriens the sinoatrial node with its automatic control of the heartbeat chemically mediated by im portant autonomic nerves which pass on the signals from the rest of the body as to its circulatory needs with particular respect to rate The volume and speed of the blood returning to the right atrium from all the body tissues also act reflexly to govern the action of the heart Besides being the pacemaker the right atrium has great capacity as a storehouse to aid in preventing the over distention of the rest of the heart furthermore the tricuspid valve is as stated by King over a hundred years ago (1837) the safety valve of the heart helping to keep it from being overloaded The pulmonary artery and its branches like the aorta by their elasticity maintain a fairly even flow of blood through the lungs instead of the forceful systolic jets both uneconomical and harmful that would be imposed on the delicate capillary structure of the pulmonary alveoli were they rigid tubes The wonderful network of tiny vessels ramifying through the lungs not only is an ideal mechanism for ex change of gases and water between blood and alveolar air but possesses such rich anastomoses between all the larger vessels and with the bronchial cir

culation that actual blocking of one of the good sized pulmonary arterial branches is not usually followed by infarction unless there are complications of serious cardiac or pulmonary disease also the pulmonary circulation in its many ramifications can hold much extra blood if necessary without great difficulty

The act of breathing not only serves for the exchange of gases between atmospheric air and blood but it has another very important and frequently overlooked function namely to suction blood from outside the thorax into the great veins by the establishment of a negative pressure on inspiration and to drive blood forward by positive pressure on expiration This is one of the important reasons for deep breathing or other exercises to keep the diaphragm and accessory respiratory muscles fit

The great elasticity and strength of the aorta and its main branches are factors of major importance in maintaining an even and economical systemic blood flow a function often overlooked Next the arterioles should be noted an amazing autonomic mechanism for the control of the circulation in any or all parts of the body dilatation brings more blood to the organ or tissues where it is needed and keeps the blood pressure from mounting dangerously while constriction helps to divert blood from any part of the body where it is not needed to other parts which are active

The capillaries first identified by Malpighi in 1661 are the vessels for which all the rest of the structures of the circulation were originally set up In their loops there is a balancing between the hydrostatic pressure and the osmotic pressure whereby oxygen needed salts and nutritive fluids seep through to the tissues and the waste products carbon dioxide and excess fluids pass back into the capillary blood stream There is a smooth and effective gradient of blood pressure all the way from the heart or aorta itself to the venae cavae

Next the veins of the body are endowed with two mechanisms that aid greatly in the maintenance of the circulation (1) the valves which normally prevent the blood from going the wrong way and (2) the proximity of skeletal muscles which by their contractions and maintenance of good tone compress the veins and help to send blood back toward the heart Thus the important accessory aid to the circulation of blood rendered by diaphragm and skeletal muscles is reason enough to keep the whole body physically fit

An interesting and essential convenience in the circulation is the portal system actually a third subdivision of the total cardiovascular tract. Here economically food products are directly taken up and stored or utilized by the liver for the body s needs

The renal circulation carries out one of the most interesting and vital functions of the body acting as a highly selective filter of the blood to rid the body of nitrogenous waste products and excess fluid and to regulate the balance of electrolytes and water Fortunately there is a great reserve for life can continue actively for many years with but one kidney Damage by infectious toxins other bacterial invasion and metallic and other poisons

accounts for most of the kidney diseases of early life To combat the acute renal shut-down in such cases there has been introduced in late years a most ingenious artificial kidney reference to which can be found in the Bibliography attached to this chapter In later life vascular changes of the renal circulation account for the slowing down of renal function sometimes with acute changes but usually with a condition called chronic arteriosclerotic nephritis

Finally the lymphatic system is a very important accessory to the circulation of blood acting to take care of all the infectious processes and foreign bodies and to perform miscellaneous tasks that cannot be readily accomplished by the cardiovascular system per se

DISORDERS OF CARDIOVASCULAR FUNCTION

And now last in our consideration of cardiovascular disease come disorders of circulatory function and rightly so for important and superficially impressive though they may often be they are fundamentally of less importance than the etiologic factors back of the cardiovascular disease and the structural defects that such etiologic factors leave behind them Disorders of circulatory function fit into two groups serious disturbances often end results of severe cardiovascular disease and trivial or at any rate relatively unimportant conditions with or without such disease Neither of these two groups should assume the major importance sometimes ascribed to disorders of function The doctor must of course recognize and properly treat these troubles but it is far more important for him to analyze and treat so far as possible the etiologic factors behind present or future cardiovascular disease in individual or family and to search for structural defects which may some day cause serious disorders of function protection against heart disease and cardiovascular failure is far more vital foresighted and profitable than the treatment of the failure itself

Although a few disorders of circulatory function are of great importance the majority are negligible or of but slight importance a careful analysis of functional disorders is essential therefore to differentiate the serious from the benign The most severe disorders which are likewise of great frequency are *congestive heart (myocardial) failure general vascular failure* and *coronary insufficiency causing angina pectoris* associated with myocardial failure are the grave conditions called *cardiac asthma* and *pulsus alternans* The first two of these disorders will be discussed in the next two chapters The third has already been discussed in Chapter 21 *Disturbances of heart rhythm* though much emphasized during the time of the development of their special study and analysis are of far less general importance than are myocardial failure and coronary insufficiency nevertheless it is necessary to recognize and to understand cardiac arrhythmia thoroughly in order to give a wise prognosis and to prescribe good treatment Disturbances of heart rhythm include premature beats (atrial and ventricular) paroxysmal tachycardia (atrial and

ventricular), atrial fibrillation atrial flutter depression of the sinoatrial pacemaker atrioventricular nodal rhythm ventricular escape (also called interference dissociation and reciprocal rhythm) atrioventricular block and intraventricular (bundle branch) block These disorders will be discussed in the three final chapters of the book Among them the only grave conditions are paroxysmal tachycardia of ventricular origin and high grade heart block both of which are rare Intelligent treatment of these and of the other disorders of heart rhythm most of which are very common affords the affected patient much relief of mind as well as of body

Circulatory failure may be subdivided in a somewhat different way from that just mentioned into the following (a) heart muscle failure secondary to specific strains such as valvular disease, hypertension and myocardial destruction which involves either left ventricle right ventricle or the whole heart (b) obstruction to the circulation with resulting congestion behind the obstruction for example congestion of the lungs from the mechanical effect of mitral stenosis and congestion of the liver from the mechanical effect of tricuspid stenosis or of acute or chronic constrictive pericarditis (c) failure of the coronary blood supply to the heart muscle (d) serious failure of cardiac rhythm due to ventricular fibrillation or cardiac standstill An interesting further subdivision of myocardial failure is into that in which there is the usual myocardial insufficiency with a decreased blood flow as in the case of hypertension or valvular disease and that in which there is increased blood flow as in the case of thyrotoxicosis beriberi arteriovenous fistula and anemia

The disturbances of normal physiology responsible for these various disorders of cardiovascular function will be taken up in each chapter under the first heading mechanism but for more detailed discussion of symptoms and signs blood pressure blood flow blood gases and graphic records the reader is referred to Part I of this book

An important part of the functional diagnosis in a cardiac patient is some sort of statement of *actual physical capacity* at the time of examination This is best expressed not by any set standards or functional tests but by the ability of the patient to carry on his routine daily activity a variable which must be considered individually for every patient A simple classification of this functional capacity is as follows

1 Full normal activity possible without cardiac symptoms
2 (a) Activity slightly restricted by symptoms
  (b) Activity moderately restricted by symptoms
  (c) Activity greatly restricted by symptoms
3 No activity possible without symptoms
4 Symptoms even at rest

Thus a complete cardiovascular diagnosis should include four features first etiology second structural change third disorders of function and fourth physical capacity The following are examples of complete diagnoses

Rheumatic heart disease with mitral stenosis atrial fibrillation and congestive failure activity greatly restricted by symptoms

Congenital cardiovascular disease with patency of the ductus arteriosus full normal activity possible without symptoms

Syphilitic aortitis with aortic regurgitation and angina pectoris symptoms even at rest

Hypertensive heart disease with activity slightly restricted by dyspnea

Although a large part of the treatment of functional circulatory disorders must be symptomatic it is equally important as I have suggested a few para graphs earlier to treat the underlying diseases when possible and especially to try to practise preventive medicine Fortunately more attention is being paid at the present time than formerly to the prevention of disease and when disease is already present to the prevention so far as is possible of the further progress of that disease and of the failure of function Such measures are especially applicable to diseases of the heart Not only must we try to abolish conditions which cause structural abnormalities of the heart but we must attempt in the presence of such abnormalities to keep strain from inducing functional disorders Here the occupational training and placement of cardiac patients is of great importance Sound judgment of all the factors involved—training mental ability physical capacity family responsibility opportunities happiness and preferences of every individual patient—must decide the matter of work for each case rather than any set of rules or standards no matter how elastic Many measures such as attendance at health resort sanitarium and spa are far more fruitful when used in a prophylactic way than when used in therapy Sound advice which is heeded is worth an immeasurable amount of medicine and the wise and careful regulation of living almost always adds to the duration of life to its fullness and to its accomplishments whether slight or serious heart disease be present

In this introductory chapter it will be of value to consider the disorders of the heartbeat from the standpoint of general classification according to rate and rhythm to supplement their individual consideration in later chapters The following tabulation gives the various types and causes of tachycardia bradycardia and arrhythmia The terminology employed throughout the book has been changed in accordance with the new international nomenclature to atrial and atrio instead of auricular and auriculo

TACHYCARDIA

Tachycardia (ταχύς quick and καρδία heart)

1 **Sinoatrial tachycardia** This consists of regular rapid heart action as a rule at rates in the adult between 80 and 160 per minute with gradual onset and offset and is generally due to the combined effect on the sinoatrial node of depression of vagal action and of stimulation of sympathetic nerve action and less often to either effect alone Rarely the rate may rise above 160 even

to 200 or more The normal heart rate of the young infant varies from 100 to 150 at rest and of the child below adolescence from 80 to 120 though there are frequent exceptions with slower rates

The causes of tachycardia are

a Normal mechanism in some healthy individuals (but not over the rate of 100 in adults at complete rest)

b Physiologic reaction to exertion ingestion of food excitement and pain

c Voluntary accleration Rare Due primarily to unusual sympathetic nerve control and attended by increase of blood pressure and by pupillary dilatation The heart rate may be doubled as from 80 to 160 The accleration is rapid requiring a few beats to full speed and not instantaneous It is still possible even after paralysis of the vagi by atropine (Favill and White 1917)

d Neurocirculatory asthenia some cases in part probably due to effort of heart to compensate for a relatively small venous blood return to the heart and in part due to apprehension

e Reaction to other factors that reduce considerably the amount of blood returned to the heart these factors include vasomotor shock hemorrhage long standing in the erect position without movement pooling of blood in extensive varicose veins and acute and chronic constrictive pericarditis

f Reaction to certain substances such as coffee tea and tobacco and to certain drugs such as epinephrine (adrenaline) via sympathetic nerve stimulation

g Reaction to drugs such as atropine causing decrease in vagal action and to diseases like diphtheria and poliomyelitis which may cause vagal paralysis

h Thyrotoxicosis

i Reaction to toxins of infections With every degree of fever there is an acceleration of approximately ten heartbeats per minute

j Reaction to pulmonary embolism

k Reaction to heart disease and failure itself

2 **Paroxysmal tachycardia** This consists of a regular rhythm at heart rates usually of 120 to 320 per minute averaging 160 with sudden onset and offset The fastest rates are found in young infants The duration of paroxysms varies from a few seconds to several days but is usually a few minutes to a few hours

The causes of paroxysmal tachycardia are primarily abnormal irritability of the heart and secondarily various exciting factors heart disease itself is not the usual cause Complete discussion of this disturbance of cardiac rhythm will be found in Chapter 32 The types of paroxysmal tachycardia are

a Atrial Usually ectopic rarely at or very near the sinoatrial node As a rule unimportant but annoying

b Ventricular Rare Usually serious

c Atrioventricular nodal Very rare Not serious

3 **Atrial flutter** This consists of a regular or regularly irregular rhythm at atrial rates usually of 200 to 400 averaging 300 and ventricular rates

usually at one half the atrial rates due to 2 to 1 heart block The onset is sudden The duration of atrial flutter varies from a few hours to several years but is usually a few days or weeks The causes of atrial flutter are as in the case of paroxysmal tachycardia abnormal irritability of the heart and various exciting factors, heart disease is usually present Atrial flutter will be discussed fully in Chapter 33

4 **Atrial fibrillation** This consists of absolute arrhythmia at atrial rates of 300 to 500 per minute averaging 400 and ventricular rates at about 150 before treatment Its onset is sudden It is usually permanent but in about one fourth of the cases paroxysmal the paroxysms lasting several hours each Heart disease is usually present in this disturbance of rhythm but sometimes the condition is wholly functional Full discussion will be found in Chapter 33

BRADYCARDIA

Bradycardia (βραδύς slow and καρδία heart)

1 **Sinoatrial** This is due chiefly to preponderance of vagal action on the sinoatrial node The rhythm is regular or irregular (sinus arrhythmia) at heart rates of 30 to 60 usually about 45 The causes are

a Normal mechanism in some individuals even at a heart rate in the 30s in a few distance runners at rest

b Physiologic reaction to rest sleep vagal stimulation by carotid sinus pressure in the neck or by ocular pressure and sometimes to cold and fright

c An occasional reaction to convalescence from certain infectious diseases for example influenza especially in youth and often after childbirth

d Reaction to increased intracranial pressure (hemorrhage tumors men ingitis)

e Reaction to certain diseases hepatitis with jaundice mumps

f Reaction to drugs especially digitalis

2 **Atrioventricular nodal rhythm,** a very rare mechanism consists of a regular heart beat at about 40 per minute the atrioventricular node con trolling both atria and ventricles It is a relatively unimportant functional disorder of unknown cause to be discussed in Chapter 34

3 **Atrioventricular block** This consists of a regular or irregular rhythm usually regular (due to 2 to 1 or to complete block) less often irregular (due to frequent dropped beats or to varying grades of block especially 3 to 2) The atrial rate is usually normal and the ventricular rate 20 to 60 being about 40 to 50 with partial block and 30 to 40 with complete block It is usually of organic origin Full discussion will be found in Chapter 34

ARRHYTHMIA

Arrhythmia (α privative not and ῥυθμός measured motion)

1 **Sinus arrhythmia** presents a heart rate usually varying with phases of respiration but sometimes very irregular It is a functional condition only the

heart may be diseased but usually it is not Further discussion will be found in Chapter 34

2 **Premature beats (extrasystoles)** may be few or many in number producing a regular irregularity as a rule they are more frequently found with slow than with fast pulse rates and without than with heart disease They are caused by excessive irritability of the heart by exciting extracardiac factors or by both Full discussion will be found in Chapter 32 There are several types of premature beats as follows

a Atrial Not followed by compensatory pause Occasional

b Ventricular Usually followed by compensatory pause Common

c Atrioventricular There is no compensatory pause if the premature beat controls both atria and ventricles but there is a compensatory pause if the premature beat is only an escape of the ventricle Rare

3 **Atrial flutter** There is cardiac arrhythmia in only about half the cases of atrial flutter and when the arrhythmia occurs it is usually a regular irregularity

4 **Atrial fibrillation** Absolute arrhythmia

5 **Atrioventricular block** The ventricular rhythm is often irregular in partial block but rarely irregular in complete block

See above under Tachycardia and Bradycardia for other observations concerning these disorders of rhythm

RELATIVE FREQUENCY OF DISORDERS OF HEART RHYTHM

To illustrate the relative frequency of the various disorders of the heartbeat shown *electrocardiographically* among individuals who consult medical advice because of cardiovascular symptoms or signs I am adding herewith the findings in the order of frequency among 10 000 patients electrocardiographed at the Massachusetts General Hospital in the sixteen years from 1914 to 1931 atrial fibrillation 1 422 cases (14 22 per cent) ventricular premature beats 974 partial atrioventricular block (including 296 cases with long *P R* intervals without dropped beats) 562 intraventricular block of lesser degrees 511 atrial premature beats 512 bundle branch block 223 atrial flutter 104 atrial paroxysmal tachycardia 80 complete atrioventricular block 79 sinoatrial block (including 18 cases of atrial standstill) 61 atrioventricular nodal premature beats 17 ventricular paroxysmal tachycardia 14 atrioventricular nodal rhythm 14 and atrioventricular nodal paroxysmal tachycardia 4 (0 04 per cent) (White and Sprague 1931)

A more recent review of the index files of the electrocardiograms of the Massachusetts General Hospital covering the nine years from February 1934 to January 1943 including 25 000 patients has shown a different incidence of disorders of cardiac rhythm doubtless due in part to the more routine use of this method of study Hence the new figures are a somewhat better indication of the true incidence of these disorders Ventricular premature beats led the list being found in 2 007 cases atrial fibrillation was second with 1 620 cases partial a v block third with 1 135 cases full bundle branch block

fourth with 1 040 cases atrial premature beats fifth with 984 cases and then in order intraventricular block of lesser grades (363 cases) atrial paroxysmal tachycardia (151 cases) atrial flutter (139 cases) complete a v block (104 cases) s a block (65 cases) a v nodal premature beats (43 cases) ventricular paroxysmal tachycardia (36 cases) a v nodal rhythm (32 cases) and a v nodal paroxysmal tachycardia (15 cases) (analyzed with the kind help of Louise Wheeler)

The relative frequency of the various disorders of the heartbeat actually experienced by patients is not fairly represented by the data obtained from the analysis of electrocardiograms since transient arrhythmias chiefly in the form of premature beats or extrasystoles are frequently missed in the short records usually taken It is quite certain from clinical analysis that ventricular premature beats are several times probably many times more common than atrial fibrillation which happened in the first series of cases noted above to be the commonest disorder found electrocardiographically also for the same reason paroxysmal atrial tachycardia is undoubtedly much more common than the figures given here suggest

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CHAPTER 30

MYOCARDIAL INSUFFICIENCY (CONGESTIVE HEART FAILURE) DIGITALIS THERAPY DIURETIC DRUGS

Even though heart muscle failure is usually a late and often the final event in the course of heart disease and so of less fundamental importance than the earlier stages and especially in comparison with preventive measures it s nevertheless a very serious condition demanding early recognition and adequate treatment Fortunately although there still remain obscurities about its pathogenesis there have been important advances both in the understanding of its mechanism and especially in its treatment since the last edition of this book

Myocardial insufficiency giving rise to congestive heart failure is the commonest of the important functional disorders of the heart It develops eventually and often terminally in more than half of all individuals with organic heart disease it also occurs in a few individuals without organic heart disease but with sudden abnormal strain as in the case of massive pulmonary embolism or of prolonged and extreme paroxysmal tachycardia in infancy

An unsatisfactory designation for severe congestive heart failure once customary in France but now being discarded was asystolie this means literally cardiac standstill which would quickly precipitate death

Mechanism (abnormal physiology) Under the effect of strain of various kinds the heart muscle may be unable to maintain a satisfactory circulation, so that vascular stasis in various parts of the body results Such stasis when it produces symptoms or signs is called congestive failure but the myocardium often weakens long before gross signs of congestion appear and various body structures and tissues such as the kidneys and the brain may suffer from a resulting lack of adequate circulation Myocardial failure may come suddenly or slowly The strain is for the most part unilateral at first and one ventricle begins to fail before the other or when both ventricles fail together the weakness of one may be preponderant Moreover failure of the left ventricle soon adversely affects the right ventricle

Failure of the myocardium has a twofold deleterious effect consisting of inadequate blood supply distal to the ventricle involved (forward failure")

and of congestion or stasis proximal to it or behind it For many years there has been much controversy as to these effects but now it is generally agreed that both points of view should be accepted and that myocardial failure acts in both ways

Failure of the left ventricle is the commonest type of heart failure It may be acute as from massive myocardial infarction or sudden tachycardia super imposed on chronic left ventricular strain or it may be gradual in its de velopment from hypertension or aortic valve disease When left ventricular failure results from the constant severe strain of chronic hypertension dilata tion occurs in the already hypertrophied left ventricle which is no longer able to pump on all the blood it receives from the right ventricle the mitral valve may or may not become relatively insufficient the left atrium is overfilled the lung vessels are engorged the pulmonary arterial pressure becomes greatly increased and the right ventricle unaccustomed to work against such high pressure which in some cases equals or even exceeds that in the systemic circu lation must increase its activity to make up for the added burden thrown upon it In such a case if the sequence of events is slow in development the right ventricle in its turn becomes hypertrophied and eventually dilates and fails along with the left ventricle Death may come however before the strain on the right ventricle has progressed so far or even before any right ventricular hypertrophy has had time to develop The significant effect on the lungs of left ventricular failure was pointed out over a hundred years ago particularly by Hope (1832)

Hope J *A Treatise on the Diseases of the Heart and Great Vessels* William Kidd London 1832

Page 196 As an obstacle to the circulation operates on the heart in a retrograde direction the cavity immediately behind it is the first to suffer from its influence Accordingly all the impediments seated in the aorta its mouth or the arterial system act primarily on the left ventricle which being likewise exposed to the heaviest burden when the circulation is accelerated has to conflict against a greater variety of exciting causes of hypertrophy than any other cavity of the heart On this account therefore as well as from the thickness of its parieties it is subject to hypertrophy in a greater degree than any other

So long as the left ventricle is capable of propelling its contents the cor responding auricle being protected by its valve remains secure Hence in a great majority of cases the auricle is perfectly exempt from disease while the ventricle is even enormously thickened and dilated But when the distending pressure of the blood preponderates over the power of the ventricle its contents from not being duly expelled constitute an obstacle to the transmission of the auricular blood Hence the auricle becomes over distended and the obstruction may be propagated backwards through the lungs to the right side of the heart and there occasion the s me series of phenomena

Page 205 The primary effect of universal obstruction of the lungs by engorge ment is to produce œdema of their cellular tissue and dyspnœa whether the latter depends solely on the engorgement or partly also on spasm of the bronchi excited by the irritation of that congestion is difficult positively to determine

though the latter is highly probable To this subject I shall revert hereafter The secondary effect is to gorge the right side of the heart and thus impede the return of the venous blood from the system at large which co operates with the increased energy of the arterial circulation in producing anasarca

Failure of the right ventricle may be more responsible in some cases for symptoms signs and even for death itself than the left ventricular failure that usually comes first If the right ventricle fails because of the strain of left ventricular failure or of chronic mitral stenosis or extensive pulmonary fibrosis it is not able to pass on all the blood it receives through the lungs to the left side of the heart it becomes dilated the tricuspid valve may be insufficient the right atrium is engorged and the blood flow in the coronary sinus the great and small veins and capillaries is hampered and often greatly slowed Dropsy or anasarca with dependent edema ascites and hydrothorax is the end stage of right ventricular failure Engorgement of the neck veins was well described as a special sign of dilatation of the right ventricle over 200 years ago by Lancisi (1728)

Lancisi J M *De Motu Cordis et Aneurysmatibus* J M Salvioni Rome 1728 page 141 (Translation by myself)

Dilatation of the right auricle and ventricle leads to two consequences worthy of the greatest consideration and these in turn lead to periodic dilatation of the jugular veins The first consequence is extreme dilatation of the venæ cavæ in which the blood may remain for a long time in copious amount Secondly the orifice of the root of the vena cava is so enlarged that the [tricuspid] valve cusps no longer close Hence it happens that with contraction of the heart blood is expelled from the right ventricle not only into the lungs through the pulmonary artery but also into the wide open superior vena cava by way of the right auricle and thence into the jugulars

Occasionally the heart fails in toto when both ventricles are affected by some common strain such as severe rheumatic carditis or severe anemia Then both ventricles dilate with resulting congestion in both the pulmonary circulation and the systemic veins the atrioventricular valves may become insufficient

Certainly the most obvious evidence of advancing weakness of either ventricle is congestion behind that ventricle in the lungs in the case of the left ventricle and in the great veins and liver in the case of the right A decrease in the power of the circulation in front of the weakened ventricle undoubtedly commonly occurs too but is much less evident clinically except under certain circumstances as in the case of the cerebral and coronary circulation in the presence of marked aortic stenosis and failure of the left ventricle and in the case of inadequate renal function on occasion when the blood pressure falls as the result of weakening of a hypertensive left ventricle even before congestion develops The most striking instance of forward failure of the circulation as a whole is that occurring in vascular collapse with resulting inadequate amount of blood reaching and leaving the heart rare cases of

extremely rapid heart rates in paroxysmal tachycardia and flutter also belong there (see Chapter 32)

Failure of the left ventricle occurs as a primary manifestation of myocardial insufficiency at least three times more often than does failure of the right ventricle That this should be so is evident when we compare the relative frequency of the factors (hyperpiesia aortic valve disease and myocardial infarction) responsible for left ventricular strain with those (mitral stenosis and pulmonary fibrosis) responsible for primary right ventricular strain (White 1933 and 1942 Boyer Leach and White 1940) that it actually is so is indicated by the far greater incidence of dyspnea in early heart failure than of engorgement of neck veins and liver

The precise way in which the heart muscle under strain dilates and fails is not wholly clear but the fundamental factor is doubtless a chemical one An excessive content of lactic acid in muscle results from excessive work and is associated with fatigue Redfield and Medearis (1926) have shown that the ability of the ventricular muscle of the turtle to develop tension is closely correlated with its content of lactic acid the more the lactic acid the less the tension possible

In the discussion in Chapter 25 on cardiac hypertrophy and dilatation it has already been pointed out that hypertrophy is probably a reaction to abnormal stretching or dilatation of the muscle fibers but from the clinical point of view except in the occasional cases of acute dilatation of the heart hyper trophy of either ventricle or of both often progresses very slowly and precedes evident dilatation and failure by a considerable length of time even by many years such hypertrophy at its onset may not be evident on examination

The three important changes that have come in the point of view concern ing cardiac dilatation and failure in the last generation of medical literature in the English language go back to some of the viewpoints of long ago swept aside by too hasty an interpretation of various findings in our own time These three changes are as follows (1) the heart is not functionally or even anatomically one organ when it is concerned with strains on any individual chamber since a single ventricle may enlarge greatly without immediate effect on the rest of the heart even though the muscle bands are continuous through out the heart and since that ventricle may itself alone fail under strain, (2) heart failure shows itself most prominently by the presence of congestion be hind the weakened chamber and not so clearly ahead of it (that is distally) although there is considerable truth in the points of view of both those who have supported the back pressure theory and those who hold the forward failure thesis—neither one alone tells the whole story and (3) there is such a thing as acute dilatation of either ventricle or of both although chronic gradual failure is more the rule

Atrial failure and dilatation are of far less importance than are ventricular failure and dilatation but they have sometimes a certain amount of signifi cance as discussed in the chapters on cardiac enlargement and atrial fibrilla- tion

Etiology *Cause* Almost any kind of heart strain can eventually cause congestive heart failure but certain factors are much more important or common than others and very often several factors are combined to precipitate failure in the same case The commonest causes of congestive heart failure are valvular defects (mitral and aortic) chronic hypertension and myocardial infarction from coronary thrombosis Less common but still very important are severe rheumatic carditis thyrotoxicosis extensive pulmonary fibrosis congenital defects anemia and abnormally fast heart rates as in long continued and uncontrolled atrial flutter atrial fibrillation and paroxysmal tachycardia. Rare causes are arteriovenous aneurysm cardiac trauma thoracic deformities external pericardial adhesions and tumors Left ventricular failure is as stated above much more commonly initial than is right ventricular failure because the left ventricle is more often subject to strain particularly as the result of hypertension narrowing or occlusion of the descending branch of the left coronary artery and aortic stenosis or regurgitation Special strains affecting directly the right ventricle are also of great importance left ventricular failure (by far the most common of all) mitral stenosis chronic pulmonary disease including emphysema and congenital pulmonary stenosis It has been suggested that bulging of an hypertrophied and dilated left ventricle via the septum into the right ventricle may be an important factor in obstructing the flow of blood through the right ventricle and so favoring the occurrence of systemic venous congestion (the so-called Bernheim s syndrome 1910), it is doubtful however, how important this is since the increased pulmonary pressure due to left ventricular failure unquestionably plays a much larger role since the right ventricle can quite readily adapt itself to changes in shape and size of the left and since pulmonary complications including embolism commonly occur in left ventricular strain and weakness and may be easily overlooked (Kinsey and White 1940)

Certain conditions act on both ventricles more or less equally such as rheumatic carditis anemia the abnormal tachycardias (atrial fibrillation atrial flutter and paroxysmal tachycardia) thyrotoxicosis generalized coronary narrowing mitral regurgitation and certain congenital defects like patency of the ductus arteriosus Special atrial strain comes with stenosis and regurgitation of mitral and tricuspid valves with ventricular dilatation and with certain congenital defects especially interatrial septal defects

In a person with heart disease failure is often precipitated by a relatively trivial circumstance such as a slight respiratory infection overeating excitement or slight overexertion but usually heart failure is of gradual onset without any particular precipitating factor In children acute rheumatic infection is the most frequent immediate cause

It is of considerable interest and value to differentiate the underlying and exciting causes of congestive heart failure An analysis of 1 000 cases (Boyer Leach and White 1940) has shown the following fundamental and precipitating factors The former were hypertension 46 9 per cent (21 3 without and 25 6 with coronary heart disease) coronary disease 41 4 per cent (15 8 with

out and 25 6 with hypertension) rheumatic heart disease 25 7 per cent syphilitic 3 0 per cent cor pulmonale 2 5 per cent calcareous aortic stenosis 1 0 per cent congenital defects 0 7 per cent and miscellaneous and unknown 2 57 per cent The precipitating factors were atrial fibrillation 14 0 per cent coronary thrombosis 12 8 per cent respiratory infection 10 5 per cent rheumatic fever 6 6 per cent pulmonary embolism 3 3 per cent other infections 1 9 per cent malignant hypertension 1 7 per cent exertion 1 4 per cent anemia 1 0 per cent thyrotoxicosis 0 7 per cent surgical operations 0 5 per cent paroxysmal tachycardia 0 4 per cent indigestion or gallbladder colic 0 3 per cent cough 0 2 per cent pregnancy 0 2 per cent asthmatic attack 0 2 per cent trauma 0 2 per cent excessive fluid intake 0 1 per cent emotion 0 1 per cent and unknown 43 9 per cent (acting suddenly in 4 8 per cent and gradually in the rest) Thus hypertension coronary heart disease and rheumatic heart disease are in the order named by far the most common fundamental causes of heart strain and failure in New England today The most common recognizable precipitating factors are first the tachycardia of atrial fibrillation second infarction of heart or lungs and third various infections in particular respiratory and rheumatic however, a large percentage of cases fail gradually without evident precipitating factor and these have the poorest prognosis

Sex Both sexes are equally subject to congestive heart failure but it occurs earlier and more severely as a rule in males Cyclical premenstrual congestion may be the first evidence of heart failure in the female

Age Congestive heart failure is found more often in old than in young persons three fourths of all the cases being more than fifty years old Nevertheless it is seen at all ages even in childhood when it is sometimes precipitated by a severe rheumatic pancarditis which interestingly enough affects the entire heart or at any rate the right ventricle so severely that the signs of the congestive failure are almost wholly limited to the systemic and portal circulations (increased venous pressure generalized edema engorged liver) while the lungs remain free (Walsh and Sprague 1941)

Pathology There are no lesions characteristic of congestive heart failure It is a functional condition which is almost invariably associated with organic heart disease A perfectly normal heart may however fail if it is under sufficient strain in such cases it is a question purely of muscle fatigue with the abnormal chemical state that exists in an exhausted muscle Much has been written about abnormality and limited reserve of the myocardium as the primary causes of heart failure while such factors as valvular disease have been considered more or less incidental this point of view is only partially correct In fact the older views that certain organic lesions were of prime importance were more nearly right than the recent teaching that the heart muscle is everything and that little else matters It is of great importance to realize that a heart muscle strong and even massive and healthy may fail simply from severe strain in its effort to overcome some defect without sign of any degeneration or inflammation as is frequently illustrated by the hypertrophied healthy

ventricular muscle in a heart that has failed from essential hypertension (hyperpiesia) and by the hypertrophied healthy right ventricular muscle in a heart that has failed from marked mitral stenosis It is this truth that has not been sufficiently emphasized in the recent past But it is also true that the heart may fail without structural defects or hypertension when there is some direct deleterious effect on the myocardium as in a severe rheumatic infection or in severe anemia Such direct myocardial effects are frequently superim posed on chronic structural lesions

The commonest structural abnormality found with congestive heart failure is cardiac enlargement consisting usually of both hypertrophy and dilatation and rarely of dilatation alone dilatation without hypertrophy is found when the failure has been acute and rapid as with coronary thrombosis or fulmi nating rheumatic carditis or prolonged extreme paroxysmal tachycardia Either ventricle may be primarily affected in the long-continued chronic cases both ventricles are involved it is of more than passing interest that by far the most common cause of enlargement of the right ventricle (beginning as hypertrophy) is chronic failure of the left ventricle and not mitral stenosis or severe chronic pulmonary disease or other factor (Thompson and White 1936) Frequently the atria are also enlarged in heart failure The myocardium shows an increased content of water in anasarca from congestive heart failure (Gross 1940) Valvular disease especially aortic regurgitation or mitral ste nosis is occasionally present Coronary arterial narrowing is sometimes found particularly in well marked cases when occlusion of the descending branch of the left coronary artery causes dilatation and failure of the left ventricle An adherent pericardium and congenital defects are much less commonly seen but they do occur in some cases Generalized arteriosclerosis and aortic ather oma often accompany congestive heart failure but they are apparently merely incidental Sclerosis of the superior vena cava has been noted as a sequel of long-continued elevation of venous pressure in chronic congestive heart failure (Gross and Handler 1939)

Summarizing the result of a postmortem study of 102 cases of myocardial failure Clawson in 1924 wrote Coronary sclerosis of serious degree was present in 22 5 per cent Myocardial fibrosis was found in a marked or mod erate degree in 20 5 per cent and in a slight degree in 30 per cent There is usually a close correspondence between the situation and the extent of myo cardial fibrosis and the distribution and degree of the coronary sclerosis Myo cardial fibrosis is usually due to coronary disease but occasionally rheumatic infections may give rise to a slight degree of fibrosis Myocardial strain (hyper tensive or nonhypertensive) is not a cause of myocardial fibrosis Syphilitic myocarditis is rare Myocardial failure is rarely due to anatomical changes in the myocardium It may be explained as an exhaustion of the cardiac muscle True chronic inflammation of the myocardium is very rare What is commonly called *chronic myocarditis is usually myocardial fatigue* resulting from the various conditions mentioned above Approximately half of the cases of myo cardial failure show no anatomical changes in the heart muscle The anatom

ical changes in the heart muscle are seldom sufficient in themselves to cause death With these statements I agree

The pathologic effect of congestive heart failure on other organs and tissues of the body is by the production of edema mostly interstitial in its site (even in the lungs) If very long-continued edema may result in actual tissue change especially in the liver but Sherlock (1951) has shown by biopsy that the liver may regenerate after damage (centrilobular hepatic necrosis) resulting from severe congestion when there is improvement in the circulation

Symptoms Since left ventricular strain is far more common than right or biventricular strain the earliest and chief symptom of congestive heart failure is usually *dyspnea* at rest or on effort not previously causing breathlessness Such dyspnea is due primarily to any one or more of several factors most commonly a reflex stimulating the respiratory center and arising in the lungs from congestion of the pulmonary circulation also the effect of oxygen lack (anoxemia) on the respiratory center and a central reflex arising from acute or subacute distention of the atria and great veins Cardiac dyspnea from the first mentioned and most common factor namely the pulmonary reflex which results from failure of the left ventricle and not of the right must be differentiated from other causes of dyspnea giving rise to such a reflex namely pulmonary pleural and bronchial diseases and one other of cardiac origin not associated with heart failure This other cardiac cause of dyspnea due to a pulmonary reflex is mitral stenosis which acts mechanically and not by myocardial failure the mitral ostium is too small to transmit to the left ventricle all the blood that comes to it from the strong right ventricle especially when there is a tachycardia from effort or excitement or of paroxysmal nature the lungs fill up as a result as was so well stated by Vieussens more than 200 years ago (1715)—see Chapter 26 The second factor namely anoxemia comes from failure of either ventricle or both and so may complicate the pulmonary reflex factor when the right ventricle fails in mitral stenosis the first factor namely that due to pulmonary engorgement is actually decreased and the second factor may change but little one way or the other since it can be caused either by pulmonary stasis or by peripheral systemic stasis

Secondary causes of dyspnea superimposed upon the primary factors are most commonly effort and excitement including the very effort of dyspnea itself which thus starts a vicious circle cough nightmares or other sudden fright paroxysmal tachycardia or atrial fibrillation pressure from hydrothorax or ascites and infections and operations

At first cardiac dyspnea comes only on moderate exertion but as the degree of failure of the left ventricle increases it comes on slight exertion and finally even when the patient is absolutely quiet Besides exertion position is an important factor in the production of dyspnea in advanced cases There are four reasons for this When the body is recumbent the blood flow through the heart is greater than in the upright position It has been reported that the effect of gravity in the upright position relieves the heart of a considerable amount (estimated at about one fourth) of the blood which circulates through it

when the patient is in the recumbent position, this reduction of work is important in giving the heart some rest Secondly and similarly, the lungs are also less engorged in the upright position Thirdly in the upright position there is more room for breathing and free heart action with the diaphragm lower and the pressure from a large liver and ascites less disturbing And fourthly in the recumbent position the respiratory center is itself directly acted on by the stasis of the venous blood in severe cases which gravity in the upright position at once helps to correct so far as the respiratory center is concerned. The symptom of difficult or impossible breathing in the recumbent position is called *orthopnea*

An important and interesting symptom of heart failure not always recognized as such may be *insomnia* due to an ill defined orthopnea in such instances treatment directed to control congestion is likely to be much more effective than the administration of hypnotic drugs which in large dosage may result in mental confusion (Wheeler and White 1945)

There is one very important and striking type of dyspnea of cardiac origin due to acute failure of the left ventricle coming on mostly in recumbency at night but also at times on effort in the daytime This is *acute paroxysmal dyspnea* which may or may not be attended by signs of pulmonary edema or by an unusual respiratory reflex resulting in asthmatic breathing When asthma complicates this phenomenon of paroxysmal dyspnea due to sudden pulmonary vascular engorgement the condition is called *cardiac asthma* Paroxysmal dyspnea due to acute failure of the left ventricle is always serious and sometimes fatal (from the associated pulmonary edema or state of shock) but there is another as a rule less grave cardiac cause of such dyspnea with or without cardiac asthma namely mitral stenosis In cases of marked mitral stenosis a sudden moderate or marked tachycardia as from the onset of atrial fibrillation which is so common in mitral stenosis tends to flood the lungs due to overactivity of the right ventricle and the respiratory distress is precipitated. Pulmonary edema due to mitral stenosis can be very serious (see Chapter 26)

Cough and expectoration with sputum which may be blood tinged are frequent with edema of the lungs interstitial and alveolar

Finally so far as disturbed breathing is concerned there is one other type not so much dependent on myocardial weakness and congestive heart failure per se as on faulty circulation in the brain itself as from marked cerebral arteriosclerosis or other cause for depression of the respiratory center This is *Cheyne Stokes respiration* with its waxing and waning of activity of the respiratory center (see Chapter 3) in well marked cases periods of apnea and hyperpnea of 20 to 30 seconds duration alternate with each other When Cheyne Stokes respiration occurs in waking hours it is a very serious sign of circulatory failure

Other symptoms of congestive heart failure are less common than dyspnea and are due in the main to failure of the right ventricle There is frequently *discomfort from congestion of the liver* more particularly if the liver engorgement is acute along with tenderness in the right hypochondrium Actually

the very first symptom of right ventricular failure is liver pain on effort due to acute congestion much as dyspnea from pulmonary congestion is the first symptom of left ventricular failure it is not however so impressive (Boyer and White 1942) Also ascites may produce disagreeable pressure sensations and edema of the legs may be painful

Pain is not common in the precordial or substernal regions but there some times is a more or less constant ache in nervous persons with big hearts Weakness is common but not uniform Insomnia headache nervousness mental disturbance and indigestion (the last from congestion of stomach liver and intestines) are frequent In a cardiac patient insomnia should always be investigated as being the possible result of dyspnea digitalis may dispel it more readily than hypnotics Palpitation is rare unless there is a complicating disturbance of rhythm

Fever has sometimes been attributed to congestive heart failure and explained as the result of the inability of the skin because of the edema and disturbance to the peripheral circulation to get rid of excess body heat Such upset of the heat regulatory mechanism of the body may perhaps account on occasion for one degree (F) of fever but fever of any significance that is of two degrees or more has been found to be due always to some complication particularly pulmonary infarction pulmonary infection or rheumatic fever (Kinsey and White 1940)

Signs The chief signs of congestive heart failure are those of blood stasis edema and cyanosis (see Chapter 4 for full discussion of these signs) Circulatory stasis may be primarily in the lungs due in the main to left ventricular failure or in liver and dependent parts of the body due characteristically to failure of the right ventricle or it may be evident in all three circulations—pulmonary portal and systemic An important factor which greatly favors the accumulation of fluid in the body in congestive heart failure is the faulty renal function due to inadequate circulation to the kidneys this results in the retention of sodium and water (see Chapter 4)

In the *lungs* the stasis shows itself first by decrease in vital capacity (Chapter 10) due to decrease in the air space often also by emphysema (the lungs being distended) and later still by moist rales beginning at the lung bases and extending throughout the lungs

In the *systemic circulation* the stasis shows itself by engorgement and visible pulsation in the neck (jugular) veins with the patient upright by increase in size of the feet and legs developing into pitting edema and eventually by an extension of edema to thighs hips genitalia abdominal wall thoracic wall and infrequently even to the arms and face Generalized edema is called *anasarca*

In the *portal circulation* stasis is shown by engorgement of the liver and by stasis distal to the liver The liver may increase enormously in size so that it reaches the level of the umbilicus or even lower in a few cases the stomach and intestines are involved also becoming congested and disturbed in function *Ascites* is found in the more severe cases The degree of portal stasis is

often out of proportion to that of stasis in the systemic circulation due probably to the greater degree of obstruction to the blood flow from the hepatic veins than to that in the inferior vena cava combined with a high degree of permeability of the capillaries of the portal system

Even though there is marked portal stasis with engorgement of the liver jaundice is found in congestive heart failure only rarely When it does occur other factors are responsible in the main acute or chronic liver damage or extensive hemolysis (as from pulmonary infarction the blood pigment from which the congested liver is unable temporarily to handle) Tests as with Bromsulphalein may demonstrate reduction in liver function during acute or chronic congestion

The accumulation of fluid in the pleural cavities (*hydrothorax*) and rarely in the pericardium (*hydropericardium*) is a further sign of congestive heart failure It is more common in the course of stasis in the systemic circulation to find hydrothorax in the right than in the left pleural cavity (McPeak and Levine 1946 White August and Michie 1947) The exact explanation of this localization is not clear it is probably due to greater stasis in the right pleural circulation than in the left either through engorgement or compression of the azygos vein or because the pulmonary circulation in the right lung has a greater height to travel to reach the left atrium than has that in the left lung especially when the patient is inclined, as so often happens to lie on the right side or because of both these factors Only a part of the left pleural circulation is drained into the vena azygos major by the vena azygos minor the balance emptying into the left innominate vein the flow in which is probably obstructed less than in the azygos veins When the fluid increases in the right pleural cavity it begins to appear also in the left and finally fluid is found even in the pericardial sac in cases with marked anasarca

Cardiac enlargement often marked in degree and sometimes acute (due to dilatation) is always evident with congestive heart failure Frequently murmurs are found due either to organic valve disease or to functional valvular insufficiency The heart sounds may be unaffected but occasionally they are of poor quality due especially to the weakness of the first sound at the apex so that with tachycardia there may be a so-called tic tac character to the sounds Now and then with marked ventricular dilatation there is heard the ominous protodiastolic gallop rhythm maximal at the apex in left ventricular weakness and at the lower end of the sternum in right Arrhythmia is frequent but is just as often absent the chief types are ventricular premature beats and atrial fibrillation

Accentuation of the pulmonary second sound often reflects the increase in pulmonary blood pressure when the left ventricle fails

Blood pressure studies with congestive failure show great variations There may be extreme hypertension lesser grades of hypertension normal pressure readings or hypotension the last being especially significant of cardiac weakness if there has been a rapid or steady fall of pressure to a low level or even a normal level from a previously high level One sign of the greatest im

portance usually discovered in the course of sphygmomanometry but often carelessly overlooked is alternation of the pulse frequently found as evidence of left ventricular fatigue even before the onset of frank congestive heart failure (see Figure 33 page 162 and Chapter 8)

Roentgen ray studies are not of great importance in congestive heart failure but they do help to determine the degree of cardiac enlargement especially if there is changing size as in a few cases with acute dilatation (with coronary thrombosis and acute rheumatic carditis for instance) they also help to show by the heart shape the type of lesion present and they afford useful information about congestion of the lungs (engorgement of the lung hilus shadows—see Figure 149—and in extreme cases even pulmonary edema) and about the presence and the degree of hydrothorax Finally fluoroscopy sometimes reveals the weak cardiac pulsations that may accompany failure

Graphic records are of some importance The arteriogram may show pulsus alternans especially after premature beats the phlebogram (jugular pulse tracing) often shows stasis by the combination of the *c* and *v* waves and the electrocardiogram may reveal some serious degree of intraventricular block or *T* wave change findings which are helpful in prognosis The electrocardiogram furthermore quickly gives information about arrhythmias and atrial action and it is frequently a useful guide in the course of treatment changes in the *S T* segment and *T* wave (see Chapter 9) and in the ventricular rate (in atrial fibrillation) affording a control of digitalis therapy The *QT* interval which is a measure of ventricular systole is prolonged in congestive heart failure and shortened by effective therapy consisting of digitalis or other measures such prolongation is probably to be ascribed in large part to the attendant cardiac enlargement chiefly dilatation for digitalis does not shorten systole in normal persons (White and Mudd 1929 Phang and White 1943)

The basal metabolic rate is somewhat elevated with congestive heart failure even to as high as 40 per cent above normal in a few cases the reasons for this elevation if thyrotoxicosis can be ruled out (which is usually done easily) are that dyspnea and cough are often present to increase the work of the body even though the patient is in bed and the myocardium itself as the result of its increased bulk and inefficiency is consuming much more than its normal share of oxygen The blood is not remarkable With considerable renal stasis the urine more or less regularly contains albumin and casts and is decreased in amount (oliguria) and renal function tests may show marked renal insufficiency for example the phenolsulfonphthalein or red test may give readings as low as 10 or 20 per cent in two hours with delayed appearance of the dye in the urine compared to the normal two hour excretion of 60 to 70 per cent and rapid appearance of the dye Also the congested kidneys are unable adequately to excrete salt With restoration of myocardial sufficiency the urine tends to clear and renal function shifts toward normal

The rate of the circulation is slowed in congestive heart failure through the lungs in left ventricular failure and through the systemic veins in right Thus a delay in the arm to-lung time from the normal average of 6 seconds to a

reading of 12 seconds as determined by the injection of ether (see Chapter 10) indicates congestion in the systemic venous circulation the most common cause of which is right heart failure If the arm to lung time is relatively normal

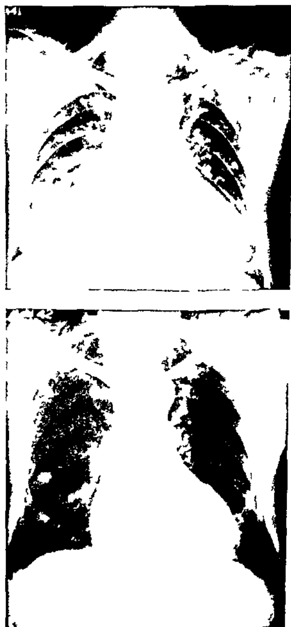


FIG 149 Roentgenograms of the thorax during left ventricular failure and following recovery therefrom Note abnormally large heart and pulmonary edema in *A* with clearing of the pulmonary edema and decrease in heart size after 9 days of treatment in *B* M B., female age 44 with hypertensive heart disease (B P 190 systolic and 150 diastolic)

but the arm to-tongue time is delayed from the normal average of 12 seconds to a reading of 24 seconds as determined by the injection of Decholin (or other test substance—see Chapter 10), we have evidence of considerable congestion in the pulmonary circulation commonly ascribable to left ventricular failure or mitral stenosis but not to pulmonary disease per se or to bronchial asthma Thus in doubtful cases of congestive failure and particularly in distinguishing between pulmonary and cardiac causes of dyspnea these circulatory rate tests are of considerable value

The output of blood by the heart is decreased and the volume of circulating blood is increased in congestive heart failure both values returning to normal on recovery

Exercise tests of various sorts have been recommended to determine the presence and degree of congestive failure the amount of dyspnea and persistent tachycardia and hypertension after stair climbing walking running weight lifting or respiratory tests have sometimes been considered as criteria of the sufficiency of the circulation As outlined in Chapter 10 these tests are of but limited value measuring as they do physical fitness as a whole rather than cardiac strength in particular The determination by inquiry or observation or both of the patient s reaction to the usual demands of his or her own particular daily life is easier less harmful and more accurate and instructive than is judgment of the heart condition by special exercise and respiratory tests

Finally there is one further method of study of some value rather in following the condition of a given case with congestive heart failure already present than in determining its presence in the first place This method is the measurement by spirometer of the vital capacity of the lungs (amount of air that can be expired after the greatest possible inspiration) The amount of the vital capacity normally about 4 to 5 liters in the male and 3 to 4 liters in the female varies inversely with the amount of congestive failure provided other factors such as inexperience in the use of the test and changing pulmonary disease do not enter in Starting at 0 5 to 1 liter during a period of marked failure the vital capacity may increase rapidly or slowly almost to normal when dyspnea is dispelled by rest digitalis and diuretics To determine the presence of congestive heart failure in the first place vital capacity studies are less useful than other methods in particular history taking

Course and prognosis Although congestive heart failure is always important its course and prognosis vary tremendously with other factors Thus contrary to some impressions it is not enough to know that the heart is unable to maintain a sufficient circulation it is as I have emphasized before important and often essential to know what conditions are causing the myocardial insufficiency in order to render a reasonable prognosis and to outline the best plan of treatment For example slight congestive failure due to chronic hypertension or mitral stenosis may be easily controlled for many years by moderate restriction of activity and digitalis therapy while congestive failure slight at first but rapidly increasing with syphilitic aortitis and aortic regurgitation or with coronary occlusion demands a far graver prognosis life often lasting but

a few months to a few years at best with much more restriction of activity and in the case of syphilis with the need of specific therapy if the cardiac condition allows There are many variables in judging congestive failure—speed of onset severity, underlying cause, age of the patient response to treatment and the faithfulness of the patient in maintaining the necessary treatment Every case must thus be considered individually from all points of view and after careful and complete study A snap diagnosis of cardiac insufficiency by a history of dyspnea and by observation of cyanosis and engorged veins in the neck is inadequate it is based on but a small though important part of the situation the end result of serious heart disease and heart strain A detailed prognostic analysis of congestive heart failure has revealed that marked cardiac enlargement, old age and the presence of the more serious uncontrollable precipitating factors and complications are the most unfavorable findings (Boyer Leach and White 1941)

To estimate an average duration of life after the onset of congestive failure is misleading because of the great variations that exist but the severity of the condition in general is shown by the fact that such an average is but a few years Many old persons have dyspnea the first evidence of congestive failure for many years without desire or need of seeking medical advice and the fact that such cases frequently are not included in statistical studies makes any estimate of duration of life after the onset of congestive failure very difficult.

There is, however one condition in the course of congestive heart failure that carries with it a serious and sometimes rapidly fatal prognosis That is paroxysmal dyspnea with or without cardiac asthma life often lasts but a few months and at best but a few years after the first attack except rarely but life can undoubtedly be much prolonged by adequate therapy especially digitalization and limitation of physical strain

Death in congestive heart failure rarely comes from the failure alone but is almost invariably due to some last straw most commonly pulmonary infarction or infection which may be difficult to diagnose ante mortem

Complications The complications of congestive failure are varied the congestive failure itself is a frequent complication of many conditions already noted Circulatory stasis disturbs the function of many organs lungs liver stomach intestines kidneys and brain Undoubtedly the coronary circulation is also often interfered with to aggravate still further the myocardial weakness Engorgement of the pulmonary circulation and edema of the lungs not only are a menace to life through asphyxiation but so affect the lungs themselves that they are easy prey to extensive hemorrhagic infarcts on the occasion of pulmonary embolism which is one of the most common and important complications of heart failure arising as it does from phlebothrombosis du to stasis in the legs (see Chapter 28) Chronic stasis in the liver can lead to atrophy and compensatory hyperplasia with the end stage of cirrhosis in some very chronic cases of mitral stenosis (and constrictive pericarditis) Gastric stasis predisposes to ulcers of the stomach and intestinal stasis to chronic in digestion and emaciation and to hemorrhoidal venous engorgement. Renal

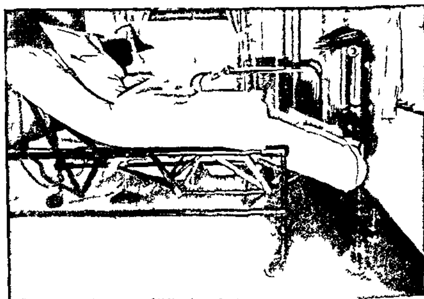
stasis can cause albuminuria renal insufficiency nitrogen retention and even rarely uremia Splenic stasis is apparently less important Congestion of ovaries and testes may cause decrease in function sterility miscarriages and disturbances of menstruation (amenorrhea menorrhagia and metrorrhagia) Massive edema of the extremities may result in ulceration of the skin and infection Cerebral edema and insufficient circulation can cause a sluggish mental state and even delirium and coma in old persons who have narrowed arteries if they have already a tendency to an unstable mentality Finally terminal infections particularly pneumonia are common in the weakened condition of patients with congestive heart failure

Treatment The treatment of congestive heart failure may be conveniently divided into seven parts as follows (A) rest (B) use of digitalis and allied drugs (C) diuretic drug therapy (D) use of other drugs including cathartics and hypnotics (E) the regulation of diet (salt and fluid intake) (F) other therapeutic measures including venesection and (G) environment and other factors Attention has already been called to the fact that in a case of congestive heart failure it is not enough simply to treat the failure it is essential from the standpoint of intelligent treatment to discover when possible what is back of the failure as for example thyrotoxicosis

A **Rest and exercise** The two most important remedies that we possess for the relief of congestive heart failure are rest and digitalis (or strophanthin) therapy All other measures though occasionally lifesaving and often useful are in general far less valuable The amount of rest to be prescribed depends on the individual case For patients who have dyspnea on moderate exertion only there need be merely slight restriction to avoid the exertion which produces symptoms sometimes however a period of a few weeks of complete rest is wise in such cases to build up reserve strength and to prolong life It is necessary to differentiate carefully in such mild cases between the dyspnea of heart failure and that of poor general physical condition or neurocirculatory asthenia when more exercise rather than less may be advisable Also it is important usually to allow a patient with heart disease but without failure to take as much exercise as he reasonably and safely can with periods of rest as needed because it is physical exercise that helps to maintain a state of general good health undoubtedly the proper functioning of the peripheral circulation and of the diaphragm resulting from reasonable exercise aids the heart in its work The most practicable exercise is walking and this is also uniformly satisfactory it can be graded easily by three factors—distance speed and slope (hill climbing) Other mild exercises like easy golf and croquet may be encouraged at times

When there is a definite amount of congestive failure at rest or on very slight exertion exercise including sexual intercourse must be prohibited and absolute rest at least for a few days should be prescribed This rest should not be maintained recumbent for as already stated the recumbent position is not a restful one so far as the heart is concerned An upright or semiupright position in comfortable chair or adjustable bed is the best arrangement for

obtaining the full benefit of absolute rest a special cardiac bed such as that shown in Figure 150 is particularly helpful for it is larger and better adapted to prolonged rest treatment than a chair and also permits ample opportunity



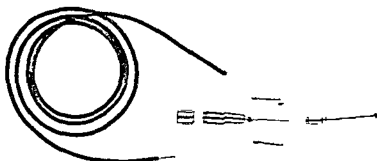


FIG 150 Photograph demonstrating the treatment of congestive failure by the "Lawson Tait" cardiac chair bed (Lewis) and by Southey tubes The bed is shown with the head partly raised and the foot partly lowered about midway between the possible extreme positions of flat bed and chair The Southey tubes are inserted in both legs or feet (usually two tubes in each) so that they drain edema fluid by gravity into bottles at the foot of the bed (the bottles may be placed in containers fastened to the foot of the bed) Penicillin is given to prevent infection during their use The tubes have small holes or slits through which the fluid passes by capillary action from the subcutaneous tissue into the fine rubber tubing A trochar the handle of which holds the tubes when not in use is employed to insert the tubes vertically into the skin and subcutaneous tissue up to their cuffs over which the rubber tubing fits The trochar and tubes are reduced to 2/5 natural size

for changing the patient s position easily There is a great difference between ordinary rest in bed and absolute rest and this difference may mean the dif ference between failure and success in the treatment of serious congestive failure With ordinary rest in bed the patient moves about a good deal by himself reaches for various things feeds himself holds a book to read some times writes or dictates and often entertains visitors With absolute rest he does as little as possible himself and is very carefully nursed he is lifted to different positions is fed is not allowed to reach for objects or to hold them to read or to write, he is denied all but a very few visitors of calming and pleasing influence the stimulating effect of noises is reduced to a minimum to while away some of the waking hours entertaining light and restful literature may be read to him for short intervals all business and family cares are banned It is not always easy to start such a regime but with full explanation of its nature and purpose and sometimes with the help at first of sedatives such as bromides or of hypnotics if needed the absolute rest therapy may prove a great success *Generally a few days of such treatment suffice along with drug* therapy when improvement is marked more activity may be allowed A mild climate is helpful during convalescence

B **Digitalis,** or foxglove either the purple (purpurea) or the yellow (lutea and lanata) is one of the most valuable of drugs its intelligent use is a real triumph in the practice of medicine permitting the accomplishment of results not possible by unaided nature Up to 175 years ago digitalis introduced as a medicinal herb and given its name by Fuchs in 1542 had been applied ex ternally as a counterirritant or used internally as an emetic and purge by the medical profession when used at all In 1785 Withering formally introduced it in the treatment of edema having discovered in 1775 that it was one of the ingredients of an herb mixture used successfully in the treatment of obstinate dropsy by an old woman in Shropshire England He enunciated clear rules for its use which however were followed but little during the next century and it has been only during the last generation that its true worth has been appreciated

Withering William (1741-1799) Shropshire England *An Account of the Fox glove and some of its Medicinal Uses With Practical Remarks on Dropsy and Other Diseases* M Swinney Birmingham 1785

Pertinent quotations from this important volume including therapeutic direc tions are as follows

After having been frequently urged to write upon this subject and as often declined to do so from apprehension of my own ability I am at length compelled to take up the pen however unqualified I may still feel myself for the task

The use of the Foxglove is getting abroad and it is better the world should derive some instruction however imperfect from my experience than that the lives of men should be hazarded by its unguarded exhibition

Fuchsius in his hist stirp 1542 is the first author who notices it From him it receives its name of *Digitalis* in allusion to the German name of Fingerhut

which signifies a fingerstall from the blossoms resembling the finger of a glove

In the year 1775 my opinion was asked concerning a family receipt for the cure of the dropsy I was told that it had long been kept a secret by an old woman in Shropshire who had sometimes made cures after the more regular practitioners had failed I was informed also that the effects produced were violent vomiting and purging for the diuretic effects seemed to have been overlooked This medicine was composed of twenty or more different herbs but it was not very difficult for one conversant in these subjects to perceive that the active herb could be no other than the Foxglove

Withering reported 163 cases treated with digitalis some of which were successful and some not The dropsies were usually treated successfully while uncomplicated cases of tuberculosis remained unchanged

Withering noted communications from correspondents citing cases A letter from Mr Wainwright a surgeon in Dudley had the following recommendation Collect it in a hot dry day when the petals fall and the seed vessels begin to swell The leaves kept to the second year are weaker and their diuretic qualities much diminished It will therefore be necessary to gather the plant fresh every season

Withering himself proceeded the more we multiply the forms of any medicine the longer we shall be in ascertaining the real dose Foxglove when given in very large and quickly repeated doses occasions sickness vomiting purging giddiness confused vision objects appearing green or yellow increased secretion of urine with frequent motions to part with it and sometimes inability to retain it slow pulse even as slow as 35 in a minute cold sweats convulsions syncope death

Directions for use I give to adults from one to three grains of this powder [powdered leaves] twice a day In the reduced state in which physicians find dropsical patients four grains a day are sufficient

If liquid medicine be preferred I order a dram of these dried leaves to be infused for four hours in half a pint of boiling water adding to the strained liquor an ounce of any spirituous water One ounce of this infusion given twice a day is a medium dose for an adult patient or once in 8 hours or ½ ounce at a time About 30 grains of the powder or eight ounces of the infusion may be taken before nausea commences

Let the medicine therefore be given in the doses and at the intervals mentioned above let it be continued until it either acts on the kidneys the stomach the pulse or the bowels let it be stopped upon the first appearance of any one of these effects

Inferences

I That the Digitalis will not universally act as a diuretic

"IV That if this fails there is but little chance of any other medicine succeeding

"IX That it has power over the motion of the heart to a degree yet unobserved in any other medicine and that this power may be converted to salutary ends"

1 *Action of digitalis* The action of digitalis on the heart is threefold (a) In the first place it depresses the pacemaking function of the sinoatrial node and also of the atrioventricular node with the resulting tendency for the heart rate

to be slowed when there is normal rhythm or in rare cases when there is atrioventricular nodal or idioventricular rhythm This is in part at least a vagal effect and may be removed by paralyzing the vagus nerves by atropine sulfate 1 to 2 mg ($\frac{1}{60}$ to $\frac{1}{30}$ gr) subcutaneously In different individuals there is often a variation of the degree of influence of digitalis on the rate in normal rhythm When this depressing effect is not very apparent it can sometimes be easily brought out by pressure over the right carotid artery Sinus arrhythmia as well as sinoatrial bradycardia are common results of digitalis action These effects of the drug on the pacemakers of the heart enter little or not at all into therapy but they should be known for they explain some of the by-effects of the drug action There are some cases of the Morgagni Adams Stokes syndrome due to paroxysmal heart block which is set off when the normal sinus rhythm rises to a rate say of 80 at which the a v junctional tissues are unable to conduct the impulses it may be possible in such cases by the careful use of digitalis to keep the sinus rate below this critical level without further depression of a v conduction In rare cases with large doses of digitalis it is even possible to paralyze the atria altogether or to irritate the atrioventricular node so that it escapes from atrial control and gives rise to a regular independent ventricular action at normal or somewhat elevated rate

(b) A second effect of digitalis on the heart is on conduction This occurs all through the heart muscle with increase in the refractory period of atrial and ventricular muscle so that atrial flutter for example is converted into atrial fibrillation (Chapter 33) intra atrial block and intraventricular block (of either bundle branch generally of slight degree) as evidenced by changes of the *P* and *QRS* waves of the electrocardiogram (Chapter 34) have in rare cases been ascribed to the digitalis effect The most marked and important influence on conduction however is on the main tract between atria and ventricles namely the atrioventricular node (of Tawara) and bundle (of His) Various grades of atrioventricular block are easily induced by digitalis from slight delay in conduction up to complete block in susceptible individuals Again the effect is in part vagal but apparently only in part for vagal paralysis often fails to obliterate the effect of large doses of digitalis Vagal stimulation (by carotid sinus pressure) usually increases easily the grade of block already produced by digitalis or brings it out when latent The effect of smaller doses of digitalis is apparen ly largely vagal the heart rate escaping to high levels as the result of sympathetic stimulation from exercise or excitement while large doses have a direct nonvagal effect which may be necessary to keep the heart rate really under control

It is this depressant influence of digitalis on conduction that explains half the virtue of the drug It has long been known that there is one type of patient with congestive heart failure especially helped by digitalis therapy sometimes with astounding success this type is the patient who has also atrial fibrillation with more or less rapid ventricular rate As noted in Chapter 33 atrial fibrillation is at the very first accompanied by a certain degree of atrioventricular block the ventricles being unable to respond to the atrial rate of 400 more or

less per minute This irregular grade of atrioventricular block is quickly increased by digitalis in full dosage and the heart rate falls to normal or even to low figures with a great increase in the intervals of rest for the ventricles (long diastolic pauses) and usually with coincident striking relief of the symptoms and signs of congestive failure The reduction of rate of as much as 100 beats per minute which sometimes occurs in such cases for example from 160 to 60 means sparing the heart muscle an unnecessary and often ineffective amount of labor consisting of 6 000 beats an hour or well over 100 000 beats a day Even a reduction of but 50 beats which is very common say from a rate of 120 to one of 70 means an omission of 72 000 contractions a day This is obviously a tremendous relief for an overworked heart There is no wonder that apparently miraculous recovery sometimes results With atrial flutter digitalis is often very useful in reducing a fatiguing heart rate for example from 150, with atrial rate of 300 to 75 due to the increase of heart block from 2 to 1' to 4 to 1,' the atrial rate remaining at 300 in atrial flutter however digitalis tends to have another effect already mentioned namely to convert the flutter into fibrillation by the production of intra atrial block with the ventricular rate still well controlled by the drug action on atrioventricular conduction With normal rhythm this influence of digitalis on conduction is usually but slight and often not evident at all

(c) A third effect of digitalis on the heart is on contraction In some manner not yet understood the tone of the heart muscle and the completeness of contraction when there are dilatation and failure are much increased by digitalis These effects in man are far more apparent in cases of normal rhythm with congestive failure than in patients with atrial fibrillation where they may be masked by the effect of the fall in heart rate It has been sometimes erroneously thought and taught that digitalis therapy is effective only in the presence of atrial fibrillation in the manner described in the paragraph above Digitalis is often though as a rule less dramatically effective when there is congestive failure with normal rhythm To withhold digitalis from such cases on the mistaken notion that it will be ineffective constitutes an important therapeutic error To be sure digitalis therapy in the presence of normal cardiac rhythm is not always effective and its success averages below that when atrial fibrillation is present nevertheless it is often strikingly beneficial and sometimes it is life saving The effect of the drug on contraction undoubtedly plays some part also in the improvement of cases of atrial fibrillation under digitalis therapy along with the reduction of heart rate Even in the presence of atrioventricular block of high grade the increase of contractile power may control congestive failure without any danger though the degree of block should be followed closely and the drug used with great caution if there is any threat of the Morgagni Adams Stokes syndrome The myocardial effect of digitalis is further shown by depression of the *S T* segments and *T* waves of the electrocardiogram

The effects of digitalis on the rest of the body are varied As a rule they are absent or slight until large doses have been administered Some of the effects

are reflex due to the action on the heart but some are direct effects on nervous and other systems

One of the apparent effects that has been noted by several investigators is that on the veins both systemic and portal with constriction acting to aid in the return of blood to the heart

Serious *toxic effects of digitalis* on the heart may occur if overdosage is allowed but such extreme effects are rare Atrial paralysis atrial fibrillation various high grades of heart block a coupled rhythm due to ventricular premature beats every second beat idioventricular rhythm ventricular paroxysmal tachycardia and ventricular fibrillation have all been induced in man or in animals by massive doses of digitalis When any of these disorders of cardiac mechanism are found to result from the digitalis given and not primarily from other factors the drug should be discontinued for a high percentage (50 to 90 per cent) of the lethal dose has probably been given by the time such disorders are found It is also of interest and importance to know that vigorous diuresis in a digitalized patient may release enough additional digitalis into the blood stream from the tissues of the body to produce temporary toxic effects

The earliest and commonest systemic toxic symptoms are malaise headache anorexia and nausea Later on, vomiting visual disturbances diarrhea and even cerebral disturbances may occur If any of these symptoms are pronounced the drug should be omitted for a while and then resumed with care It is important always when searching for toxic symptoms to inquire whether there is blurring of vision or disturbance of color vision—in the latter case objects appear usually yellow or green (Purkinje 1839) Such visual disturbance may be present but not complained of at once being masked perhaps by other toxic symptoms Finally there are individual variations in the ease with which digitalis produces toxic as well as beneficial effects every case must be considered individually

Allergy to foxglove is excessively rare It has been reported (Cohen and Brodsky 1940) but I have not encountered an instance myself among a good many thousand cases The patients whom I have seen who have been easily nauseated or otherwise upset by the drug are those who dislike the taste even when coated tablets are used (regurgitation still gives them the taste) or dislike the idea of taking the drug at all or those who have previously been made sick by it which is evidence of the wisdom of avoiding overdosage to start with and of the art of persuasion when the drug is badly needed

2 *Therapeutic indications for the use of digitalis* There are five chief indications of the need of digitalis therapy (a) congestive heart failure with or without atrial fibrillation atrial flutter or heart block (b) atrial fibrillation or atrial flutter with rapid ventricular rate when quinidine sulfate alone is not administered at once (see Chapter 33) (c) obstinate paroxysmal tachycardia or premature beats which may infrequently be abolished by digitalis (d) as a therapeutic test when it is uncertain whether or not there is a slight degree of congestive failure as in the case of old persons with slight dyspnea on exertion of victims of chronic pulmonary emphysema with a higher degree of

dyspnea than is readily attributable to the lung condition alone and of patients with massive pulmonary embolism and (e) as a means of delaying or warding off heart failure altogether and even perhaps of preventing further cardiac enlargement in patients with serious chronic heart strain from any cause who already have big hearts For other conditions digitalis should not be used much of it has been wasted in the past and many patients with all manner of illnesses have been made at least temporarily miserable by the toxic effects of digitalis with no resulting benefit The drug should not be used in any way routinely in preparation for surgical operations (unless there is serious heart strain congestive failure or atrial fibrillation) in the treatment of surgical or postoperative emergencies and collapse during anesthesia in the therapy of infectious diseases or in treating constrictive pericarditis (acute or chronic) in the absence of atrial fibrillation or flutter or neurocirculatory asthenia The indiscriminate use of digitalis is to be strongly deprecated

There are no contraindications to the use of digitalis when the drug is really needed except the very rare Morgagni Adams Stokes syndrome in high grade heart block (even in such cases there are exceptions—see page 943) and the very rare individual hypersensitivity to the drug action Complete heart block without syncopal or faint attacks is not a contraindication

3 *Preparations of digitalis* The ways in which digitalis is prescribed have varied very much with the years After its introduction by William Withering and for a hundred years or more it was used mostly in the form of the dried leaf and in tinctures and infusions At the beginning of the present century the tincture and powdered dried leaf were used chiefly Gradually the tincture itself has been largely given up in this country so that pills or capsules of standardized dried leaf have been in current use more or less routinely during the last two decades and have proved a very satisfactory way of giving digitalis However during recent years purified active principles and extracts of digitalis derived from the purple and yellow foxglove have come more and more into use and have the advantage of less need of animal standardization and of simple use by weight alone An interesting preparation for investigative purposes has been introduced by growing radioactive digitalis in an atmosphere of radioactive carbon dioxide (Geiling et al 1949)

In the previous editions of this book there has been considerable reference to cat units and to the use of frogs for the standardization of digitalis Fortunately in the future although such testing is still necessary when one uses the whole leaf it will become less and less necessary to refer to such standardization in discussing treatment with digitalis In the evolution of the improvement of digitalis preparations a generation ago the strict insistence on some method of standardization helped greatly in getting rid of inert preparations on the market (Pratt and Morrison 1919) Human standardization has been recommended (Gold et al 1942) and as a matter of fact is actually the best method of all in dealing with preparations in need of testing despite its practical difficulty and the considerable variations of sensitivity in individual subjects

These extracts of digitalis more currently in use today include one of the very old purified glycosides first introduced over a hundred years ago by Nativelle (1845) This is digitoxin also called Digitaline Nativelle Purodigin and by other trade names It is an effective preparation almost a thousand times stronger in its effect by mouth than standardized dried digitalis leaf so that 0 10 mg of digitoxin is approximately equivalent to 0 10 gm of dried leaf It is my experience however that it is not so strong and that for the human 0 15 mg of digitoxin is equivalent to 0 10 gm of digitalis leaf Other active principles include digitonin digitalein digoxin Digalen and lanatoside C (Digilanid from digitalis lanata)

One of the chief advantages of these purified preparations is that they can be more readily given intravenously in full strength Digitoxin for example given intravenously has much the same effect as when given by mouth The method of administration and exact dosage will be referred to below

4 *Method of digitalis administration and dosage* There has been considerable confusion in the past as to the strength of digitalis leaf in the *U S Pharmacopeia* To follow the international standard it was necessary to increase the strength per weight of the drug at the time of U S P XI (1936) and U S P XII (1942) from that of the previous standard of U S P X (1926) The result of all this change was that the standard strength of digitalis leaf now as compared with the strength twenty years ago is in the ratio of 85 to 1 00 thus a grain of digitalis leaf now is equivalent to 0 85 gr of twenty years ago and a dose of 1 5 gr is equivalent to 1 28 gr of the earlier strength Because of the greater ease of slow digitalization years ago than now one preparation namely Digitora (Upjohn) has held to the old dosage and consists of 1 28 and 0 85 gr tablets for convenience in routine use as will be discussed below under dosage At first when this change in strength took place there was a good deal of digitalis intoxication because of the failure of the medical profession in general to be aware of the greater strength of the preparations this situation has now been largely corrected

The methods of digitalis administration are several The most common and generally useful is by mouth applicable to at least 95 per cent of all cases needing the drug Parenteral injections into vein or muscle and rectal suppositories should be reserved for the very few cases in which the drug is urgently needed and cannot for some reason be given by mouth

There are three important aspects in the matter of giving digitalis (1) digitalization that is saturation with the drug (2) maintenance of its effect (3) testing its value in a given case Also there are various methods namely (1) the common oral administration (2) the infrequently needed intravenous use and (3) rectal administration

Digitalization consists in the administration of enough of any digitalis preparation to obtain the maximal therapeutic effect with as little toxic action as possible Such digitalization may be rapid or slow and by mouth or by vein Very few patients especially in these days of more enlightened treatment require emergency rapid digitalization When this is necessary the intravenous

route is generally the most suitable However the result may be quite satisfactory by oral medication provided a rapidly acting drug is used Figure 151 illustrates the speed with which digitalization can be secured within a few hours by intravenous medication with certain preparations for example lanatoside C or Cedilanid and ouabain or strophanthin A dose of 0 8 mg of Cedilanid (1 cc = 0 2 mg) repeated in full or half dosage in four hours if necessary is an effective method of rapid digitalization 0 5 mg (½ cc solution) of strophanthin or ouabain is also effective and somewhat more rapid in its action In each case the effect begins in a relatively few minutes reaching its maximum within a few hours, the exact time varies somewhat from patient to patient Digitoxin may also be given intravenously in the initial dosage of 0 6 mg to 1 2 mg or more for full effect quite rapidly, the special advantage of digitoxin is that it can be given in the same dosage also by mouth with somewhat slower but usually satisfactory result in the course of a relatively few hours Digitoxin when given by mouth is absorbed essentially in toto and therefore can be used in uniform doses

Standardized digitalis leaf in powdered form may also be used for digitalization by mouth Its strength is about a thousandth of that of the pure digitoxin and therefore, in the course of twenty four hours about 1 2 gm need to be given Since each pill of digitalis is conveniently put up in 0 10 gm (1½ gr) the total amount may be given in the form of 0 3 gm that is three pills four times in twenty four hours or even 0 4 gm at a dose at four hour intervals, thus getting in the full amount in the course of eight hours which is rapid enough for the great majority of patients needing quick digitalization The advantage of divided dosage of any of these preparations is that some individuals are very sensitive to the drug no matter in what form it is given if there are toxic effects after the first second or third dose the later doses may be reduced or omitted It is important to try to avoid serious toxic effects from digitalis because of the common need for the constant use of digitalis for weeks months or years after it has once been given Happily digitalis is as effective after ten years as it is the first day There is not the acquirement of tolerance to the drug hence no need of increasing the dosage with the passage of time as in the case of so many other drugs Most of the so called allergy or sensitivity of patients to digitalis is the physical or psychologic repugnance to the drug following a toxic effect I myself experimentally took large doses of digitalis over twenty years ago and I still have a strong memory of the disagreeable taste at the time of toxic symptoms from it Therefore the one dose method of digitalization is generally to be avoided unless the situation is very critical otherwise and we are dealing with a large patient who is apparently not hypersensitive to medicines in general

Preparations of the whole leaf, for example Digifolin are also available for intravenous use and may be given thus in about the same dosage and time intervals as the pills by mouth

For slower digitalization it is very convenient to use one week s time for saturation with the drug for example one may prescribe the medicine to an

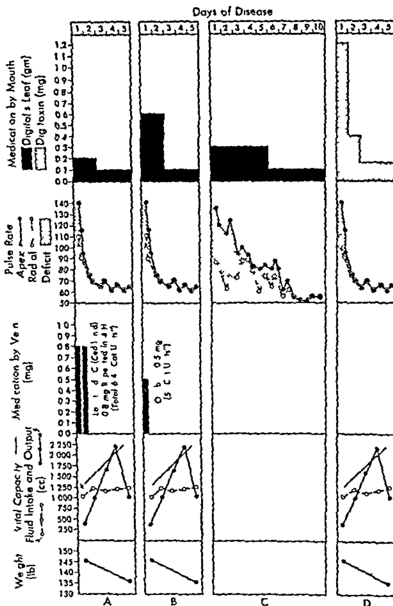


FIG 151 Charts showing the effects of digitalis in congestive failure and atrial fibrillation with particular reference to heart rate clearing of pulse deficit (shown by shading above) fluid balance vital capacity and weight (*A*) Rapid effect during the first day of treatment by means of digitalis given intravenously followed by powdered digitalis leaf by mouth The dosage is indicated on the chart (*B*) To illustrate essentially the same results to be expected by the use of ouabain intravenously followed by digitalizing dosage of powdered leaf by mouth (see text for comparison of the effects of ouabain and digitalis given intravenously) (*C*) Slower but effective digitalization in a case of atrial fibrillation without congestive failure by powdered digitalis leaf by mouth Dosage indicated on the chart (*D*) Effective rapid digitalization of atrial fibrillation by digitoxin given orally

ambulatory patient in hospital clinic or private office and have the patient return in one week to determine the effect For this purpose the digitalizing dose may be spread through the seven days adding a little extra for excretion each day Thus if one uses dried whole digitalis leaf of the current strength one may give a 0 1 gm (1½ gr) pill twice a day for a week or three times a day for four days followed by one pill daily thereafter A few patients need slightly larger doses than this and a few patients slightly smaller but this is the average for the majority of adult patients If one uses digitoxin one may give three 0 1 mg tablets daily for a week or somewhat more the first half of the week with maintenance dosage afterward of 0 1 to 0 2 mg Digitoxin is available in 0 10 0 15 and 0 20 mg tablets I have found the tablet of 0 15 mg the most suitable of all as a daily ration in the great majority of cases

There are many other preparations of digitalis which now are all quite satisfactory for digitalization One of the most useful of all the preparations of the dried leaf is that of Digitora which has kept the old standard strength a very convenient strength for slow digitalization which after all is the best method for the great majority of patients needing digitalization One tablet of Digitora equals 1 28 gr and can be given three times a day for one week to get just about the right saturation for the average patient whereas 0 1 gm (1 5 gr) of the current strength of digitalis three times a day for a week is too much for most patients and may induce toxic and therefore undesirable symptoms at the end of the week For rapid or slow digitalization it is possible to give digitalis rectally in the form of suppositories, but these in general are not so reliable since they are not always absorbed adequately and they are sometimes irritating Hence this is the least desirable way of administering digitalis, although suitable in rare cases

A point of much concern in the past has been the question of the dosage with respect to the size of the patient and formerly much calculation was carried out from the standpoint especially of the amount of the drug needed for rapid digitalization At one time 0 1 gr of the leaf was considered necessary for every ten pounds of weight and although this in general may still hold there have been so many exceptions to the relationship of the patient s weight and dosage that we no longer bother about such accurate calculation which really is misleading For a very large person we may rightly prescribe larger doses and for a very small person a decreased dosage but the wide range of the average between these two extremes does not need to alter what has been written above and what follows below For children the dosage of course must be less for a child aged 10 to 12 years half the adult dose is to be advised and for the infant about one quarter

Maintenance of digitalis effect One of the greatest advances in the treatment of heart disease that has occurred in the last generation has been the realization of the importance of the maintenance of digitalis effect Years ago it was customary to give courses of digitalis with strikingly beneficial effect each time but with the result that between courses of digitalis there would tend to be a recurrence of myocardial insufficiency and often of severe congestive failure As time passed a few individuals became aware of the vital need of maintain

ing the full digitalis effect in almost all patients who once needed it Thus we have done away in large part with two common occurrences of the past The first was the arrival in the emergency wards of the hospitals of cardiac patients with a sudden onset of pulmonary edema or acute distress otherwise due to rapidly developing heart failure or the emergency summoning of physicians to homes or places of work to treat these people These accidents still occur but in my experience they are very much less frequent than they were twenty five to thirty years ago Second one does not see what one used to the rapidly recurrent anascara in patients who after digitalization have been allowed to escape from its effect

For the maintenance of digitalis action there are numerous oral preparations available the most common and practical being the whole dried leaf itself in tablet or pill form in the dosage of 0 1 to 0 06 gm (1½ gr to 1 gr) daily Such a tablet or pill may be given daily for weeks months or years to maintain the excellent effect as shown by the persistence of a satisfactory heart rate in the presence of atrial fibrillation or by the failure of a return of evidences of myocardial failure with congestion Some patients need the larger dose and are not made sick by it others can get along with the smaller dose better and a good many do best with a dosage in between for example 0 1 gm (1½ gr) one day and 0 06 gm (1 gr) the next day and so alternately thereafter Sometimes it is convenient to put up a capsule of 1¼ gr (0 82 gm) Also conveniently digitoxin can be used for maintenance in the dosage by tablet of either 0 2 or 0 1 or best of all of 0 15 mg daily Cedilanid may be given in daily rations of an average of 0 25 mg and digoxin in a daily dose of 0 5 mg Liquid preparations can still be used although they are much less commonly employed in this country today The tincture is a reliable preparation of digitalis consisting of a 10 per cent solution This can be given in a dose of 1 cc (15 minims) corresponding to 0 1 gm of the dried leaf the dosage of tincture by mouth can thus be calculated readily

Electrocardiographic control of digitalis therapy is often very helpful On occasion the electrocardiogram will show definite effects of digitalis action just before beneficial effects become evident and also on occasion toxic effects may appear first in the electrocardiogram in the form of bigeminy and marked depression of the *S T* segments or prolongation of the *P R* interval before they become manifest as noted above in the form of nausea vomiting intestinal irritation and disturbance of vision Figure 152 page 832 shows full digitalis effect in the electrocardiogram of a case of mitral stenosis with atrial fibrillation

Of considerable interest and importance has been the gradual development of tests of the concentration of digitalis in the blood one of the most recent of which a polarographic determination has been reported by Hilton (1949) It is to be hoped that a routine practical determination may become possible

Until recently the cost of purified preparations has been so much greater than that of the leaf in powder or tincture form that on the basis of expense many have preferred to continue with the whole leaf However as time goes on and costs come down the purified preparations will be more and more

employed because of the simplicity of the dosage without need of animal standardization

Finally on occasion it is useful to test the effect of digitalis in any given case where myocardial failure is suspected or where there is some important com

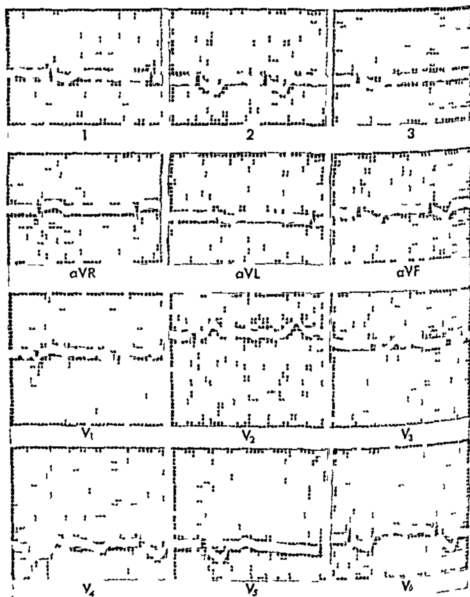


FIG 15? Electrocardiogram in atrial fibrillation with full digitalis effect male age 52 (*A*) Bipolar limb leads 1 2 and 3 (*B*) unipolar limb leads aVR aVL, and aVF (*C*) six precordial leads V to V inclusive Note especially the slow heart rate and the depressed (digitalis) *S T* segments and flattened *T* waves in Leads 1 ? 3 aVL, aVF and V to V inclusive Time = 0 04 and 0 20 second amplitude 1 mm = 0 10 mv

plication that may prevent its full action The same methods of administration as noted above that is of rapid or slow digitalization and maintenance of effect are to be employed but now and then one may want to use at the start small or moderate dosage without full saturation first Where the need is not so great full digitalization is not so urgent and some benefit may well come from smaller doses such as the so-called tonic dose of 0 1 gm (1½ gr) or 0 06 gm (1 gr) of the dried leaf daily It is difficult and sometimes impossible to prove or disprove the advantage of this but there is reason to believe that such tonic dosage in the absence of heart failure may help to prevent or delay increasing enlargement of the heart and future failure in cases of constant heart strain as from important valvular disease or hypertension

There are only two drugs besides digitalis which have digitalis like action that are of much worth They are *strophanthin* or *ouabain* and the newly standardized active *glucosides of squill* (called variously as Scillonin and Urginin)

5 *Strophanthin (ouabain)* has been proved effective in emergency treatment but its superiority over an ample intravenous dose of digitalis or its glucosides (digitoxin and lanatoside C for example) is debatable However experienced workers with strophanthin clinically chiefly those trained in the continental European and Latin American clinics report that the drug is superior to digitalis in certain cases for two reasons (1) because of its more rapid full action in emergencies (shown by Eichna and Taube 1943) particularly when the heart rhythm is normal in acute cardiac failure and (2) because it is thought to have a greater stimulating effect on a failing myocardium in the degenerative types of heart disease (hypertensive and coronary) Strophanthin or ouabain injected intravenously in the dose of ¼ to ½ mg (1/240 to 1/120 gr) never more may result rapidly in great improvement with the saving of life or the clearing of the heart failure The dose may be repeated in 12 hours and then once every day or two as a ration (⅛ to ½ mg) if necessary but it is better to begin full doses of digitalis by mouth within 12 hours of the emergency injection of ouabain so that the digitalis will become effective at a time when the transient effect of the ouabain is wearing off 0 2 gm (3 gr) of the standard powdered leaf three times daily for two days should suffice before dropping to a ration of 1 or 1½ gr daily It is largely a matter of choice and custom whether one uses digitalis or strophanthin in emergency treatment On the European continent and in South America strophanthin is often employed successfully while here in the United States digitalis has been preferred If it seems desirable to use strophanthin and digitalis has been previously given an interval of forty-eight hours should be allowed to elapse before the strophanthin is administered intravenously so that danger of poisoning may be prevented

Strophanthin when given intravenously begins to act appreciably on the heart in a very few minutes (five to twenty) with full effect probably in an hour s time and maintenance of the action for twelve to twenty four hours Digitalis given intravenously in potent dosage takes about the same length of

time as strophanthin for initial effect, or perhaps a little longer a definitely longer time for full effect (two hours) and its action lasts somewhat longer (one or two days) (Wyckoff and Goldring 1927 Pardee, 1928) Digitalis by mouth is slower to act and yet rapid enough in its effect in most cases showing definite action in two or three hours with full effect in about twelve hours and persistence of action for several days When full digitalization by mouth has been effected an interval of ten days to two weeks is necessary before all the drug disappears from the system

6 *Squill* The active principle of squill may be used by mouth advantageously *in the very few cases who need digitalis but cannot take it* because of a hypersensitive reaction or very strong prejudice against the taste It is prescribed as scillaren (Scillonin) or as Urginin in tablet form in the dosage of 0 8 mg (1/80 gr) of the former or 1 0 mg (1/60 gr) of the latter as equivalent to 0 1 gm (1½ gr) of standardized digitalis

7 *Other digitalis like drugs* Other drugs of the digitalis group including strophanthus when used by mouth are inferior to digitalis and squill in effectiveness and reliability they include apocynum and convallaria A newer drug (a cardiac glucoside) with a rather rapid stimulating myocardial effect has been introduced under the name *thevetin* it comes from the kernels of the bestill nuts of a tropical tree Thevetia nerufolia and is related to apocynum given intravenously it has had in some cases of congestive failure an effect even greater in rapidity than strophanthin (or ouabain) further study of its clinical applicability has been in progress (Arnold Middleton and Chen 1935 Chen personal communication 1942, 1949 Modell et al 1948)

Very rarely digitalis cannot be taken even in small dosage because of its poisonous effect in a particularly hypersensitive individual It is fair and advisable in such a case to try one after another of the drugs of the so-called digitalis series until one is found that is to some degree effective without being toxic It may be assumed as a general rule however that the toxic and therapeutic effects of various preparations of digitalis or of other drugs of the digitalis series are parallel a preparation that can be taken in large dosage without toxic effects is likely to be therapeutically inactive and a preparation that is very active therapeutically tends quickly to cause toxic symptoms One of the *drugs of the digitalis group namely squill has a reputation* as a diuretic but this reputation is probably based as is that of digitalis on inaccurate observation Its diuretic effect is secondary to improvement in the circulation there is no primary diuretic action Finally it is very important to remember that rest alone will frequently give rise to diuresis when there is edema

8 *Chart of digitalis effects* To follow accurately the effect of digitalis squill or strophanthin in congestive failure it is well to keep a careful chart of (1) the apex heart rate and the pulse deficit (difference between apex and radial pulse rates) especially if there is atrial fibrillation (2) the loss of weight and urine output (as compared to fluid intake) to note a diuretic action and (3) subjective symptoms of improvement (Figure 151 page 829) The vital

capacity record may also prove of interest rising with decrease in the degree of failure And finally the *T* wave of the electrocardiogram often but not always shows changes characteristic of the effect of digitalis becoming diphasic and flattened at first especially in its early part (or more exactly the *S T* segment) and eventually with full digitalization becoming deeply inverted (Chapter 9 and Figure 152) When the ventricular rate is high in atrial fibrillation intravenous strophanthin or rapid digitalization usually causes a sharp drop in rate in the course of an hour or two finally in a few hours there may be complete disappearance of pulse deficit (with even a slight rise of radial pulse rate in rare cases if such radial pulse rate was at first low because of weakness of many of the heartbeats) Along with this remarkable fall in heart rate due to the production of block in atrial fibrillation the electrocardiogram usually shows a rapid change (inversion) in the character of the *S T* segment especially in Lead 2 The diuresis that frequently results from digitalis therapy in edematous cases which incidentally was the finding that first called attention to the value of foxglove in heart disease is not the direct effect of the drug but the indirect effect of improvement of the circulation In the absence of edema digitalis has no diuretic effect

9 *Miscellaneous drugs without digitalis like action* Finally before leaving the discussion of digitalis and other members of the digitalis group mention should be made of certain unrelated drugs which have been occasionally substituted for or used in addition to digitalis in the treatment of congestive heart failure because of their supposed stimulating effect on the heart None of these drugs with one exception has been shown in any way valuable because of a direct effect on the heart The exception *epinephrine* or *adrenaline* has a powerful but transient action It has not been found valuable in the treatment of congestive failure At present its chief value rests in the revival of the heartbeat in standstill of the heart whether because of sinoatrial depression or of high grade atrioventricular block (Morgagni Adams Stokes attacks) it is of less value in the treatment of collapse or shock It sometimes helps a little in a secondary role in the therapy of an attack of cardiac asthma A recently introduced drug allied to epinephrine in action but much more gradual and persistent in effect is ephedrine (from the Chinese plant ma huang) its action in congestive failure is not favorable enough to consider its use even as an extra aid

All other so-called stimulants if active at *all* produce an effect not directly on the heart but on the nervous system blood vessels or other tissues none of them can in any way take the place of digitalis These drugs include strychnine camphor caffeine theobromine and theophylline ethylene-diamine sparteine adonis vernalis physostigmine crataegus Cardiazol Coramine aconite and cactus Caffeine has an important stimulating effect on the nervous system and vasomotor center while Coramine and theophylline ethylene-diamine (aminophylline) often stimulate and regulate a depressed respiratory center and the latter aminophylline dilates the coronary arteries and dissipates distressing Cheyne Stokes breathing and the asthmatic dyspnea in acute pul-

monary edema but they do not so far as we know have a direct myocardial action Cactus is apparently inert

C **Use of diuretics** When dyspnea (from pulmonary congestion) and edema in congestive heart failure are not quickly relieved by rest *by the effect* of digitalis or by diet and fluid restriction they usually yield to the primary diuretic properties of certain drugs At times such diuretic drugs are of great importance in maintaining comfort and prolonging life when there is congestive failure They should be supplementary to and not replace digitalis except perhaps in children with congestive failure secondary to acute rheumatic myocardial disease in whom digitalis is generally inert actually harmful or at least inferior to such a diuretic as theobromine sodium acetate (thesodate) (Walsh and Sprague 1941) The diuretics consists of mercury (and bismuth) compounds purine derivatives and various salts including chlorides nitrates and urea The most helpful diuretic drugs which have now come into routine use are the mercurials (especially Mercuhydrin) and ammonium chloride (see below)

1 *Mercury* is a powerful diuretic It was used for many years in the form of calomel (mercurous chloride) by mouth but in more recent years, much more satisfactory mercury compounds for intravenous or intramuscular or even oral use have been introduced Diarrhea and stomatitis can be very disagreeable toxic effects from the oral administration of mercury although occasionally astonishing diuresis results Following the historic use of calomel there were introduced the newer mercurial compounds Novasurol or Merbaphen (a mercury urea compound) Salyrgan or mersalyl (a mercury salicylate compound) and Mercupurin or novurit (a mercury theophylline compound) which were given intravenously or intramuscularly in the initial dose of 1 to 2 cc (of a 10 per cent solution) and then daily or at intervals of a few days to one or two weeks or longer in the dosage of 2 cc as needed (Figure 153 opposite) The last two mentioned preparations Salyrgan and Mercupurin were more effective and less toxic than Novasurol The most used mercurial diuretics today are Mercuhydrin (a mercury alluride compound) best given intramuscularly in the dosage of ½ to 2 cc Mercuzanthin (mercurophylline i e a compound with theophylline) and Thiomerin (sodium mercaptacetate) this last administered subcutaneously These mercurials can be repeated frequently on occasion even as often as daily or every other day but it is of course best to avoid excessive dosage and to increase the interval between injections as soon as possible and as widely as possible Also the smaller the effective dose the better Not infrequently ¼ to ½ cc may be quite adequate and not so exhausting as the larger doses of 1 to 2 cc Care must be used to avoid serious toxic effects but such are very rare only a few deaths have been reported among hundreds of thousands of injections although true hypersensitiveness to Mercupurin has been noted (Fox Gold and Leon 1942) Sodium mercaptacetate (Thiomerin) has the added convenience of subcutaneous administration which makes it possible for personal use by the patient himself or by one of his family

These mercurial preparations may be used with some success even for ascites due to cirrhosis of the liver Extraordinarily large amounts of these drugs have been given to a single patient with constant benefit and apparently no harm whatsoever to kidneys liver or other organs for example 240 cc of Salyrgan in 198 doses to one patient (*Maxwell Scott* and Harvey *1933*) and 270 injections over a period of five years to another (Wiseman 1932) The simultaneous administration of various ammonium or other such salts by mouth often reinforces and increases the diuretic action of the mercury preparations but if they are active themselves there may be no need of giving *these other drugs Mercury may be given by suppository also in the form of* Mercurin or Mercupurin but it is less effective and often irritating

2 *Bismuth* and *arsenic* though possessing some diuretic properties are inferior to mercury in the treatment of obstinate edema

3 Of the *purine group* caffeine itself is too weak to be particularly useful *Theobromine or theobromine sodium salicylate (Diuretin)* is one of the most

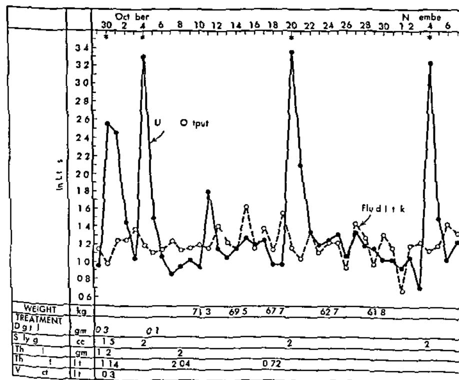


FIG 153 Chart showing the effect of the diuretic therapy of congestive heart failure in an elderly man There is especially evident the vigorous action of the mercury preparation Salyrgan (mersalyl) injected intravenously Life was prolonged in relative comfort and quiet activity for about one year in the case of this patient by the occasional use of Salyrgan digitalization alone with its constant maintenance was inadequate

Me uhyd in Mercupurin and Thiomerin may now be used in preference to Salyrgan (See text)

valuable diuretics because it is often effective and but slightly toxic It is best given in the dosage of 0 5 to 1 0 gm (7½ to 15 gr) of the salt or 0 5 gm (7½ gr) of the alkaloid in powder or tablet form three times a day for several days or weeks If effective it may be kept up constantly or it may be discontinued after an interval and then resumed again in repeated courses later for several days at a time for example every ten days or two weeks as needed *Theocalcin (theobromine calcium salicylate)* 7½ gr tablets or *Thesodate (theobromine sodium acetate)* in enteric coated tablets of 3¾ to 7½ gr or *Glucophylline* (double salt of theophylline 1 18 gr and methylglucamine 1 16 gr) may be given in the place of Diuretin In half of the cases of obstinate edema not yielding to rest and digitalis theobromine or one of its salts suffices But for other cases more vigorous diuretics are necessary These include other of the purines theophylline (or Theocin) and its derivative theophylline ethylene diamine (aminophylline) or Phyllicin which may be also given for several days trial If effective they may be resumed for intervals of a week or two as needed Either of these drugs theophylline or its derivative may be adminis tered as small daily rations in 3 gr doses three times a day but they are more likely to upset the digestive tract than are the theobromine compounds A more or less constant mild diuresis may be maintained by the use of drugs of the purine group given by mouth

The chief difficulty in the use of either theobromine or theophylline espe cially of the latter is that these drugs are very likely to produce toxic symp toms chiefly nausea and vomiting but their various salts are much better borne It may be added that theobromine and allied drugs have been given in the treatment of coronary insufficiency and Cheyne Stokes respiration sometimes with great benefit theophylline ethylene diamine (Metaphyllin or aminophylline) has been particularly effective in the control of Cheyne Stokes respiration given intravenously in the dosage of 0 25 gm (4 gr)—it is always worth trying and sometimes smooths out the breathing within a minute or two

4 Certain salts namely *ammonium chloride ammonium nitrate am monium sulfate magnesium sulfate calcium chloride* and *urea* also have diuretic properties especially the ammonium salts associated with their pro duction of a mild acidosis and resultant extraction of sodium from the body When given alone they may or may not be sufficiently active In order to pro duce an effect by themselves they have to be administered sometimes in large doses (for example 8 to 10 gm of ammonium chloride daily) and they are generally disagreeable to take As an adjuvant to mercury compounds in the treatment of obstinate edema ammonium chloride or ammonium nitrate is often helpful in the dose of 1 0 to 1 5 gm (15 to 22½ gr) four times daily The ammonium salt should be given in enteric-coated pills of 7½ gr (0 5 gm) each *Urea may be given for weeks or months effectively in* the dosage of 10 to 25 gm two or three times a day in a 40 per cent watery solution but it is not so useful Often these salts are not necessary the mercury alone proving adequate but occasionally they are quite effective and worthy of trial when the mercurial therapy is insufficient, and in some cases they may be used alone

with beneficial mild diuresis Calcium (and potassium) salts (for example calcium gluconate) in high dosage should not be administered to digitalized patients because of the hazard of serious toxic effects on the cardiac mechanism

5 Finally *parathyroid extract (parathormone)* has been found to have diuretic properties Although it mobilizes calcium in the blood it acts differently from calcium chloride which causes diuresis by producing an acidosis Parathormone has not however been used clinically to replace the other diuretics

The exact mechanism of the action of primary diuretic drugs is not always clear it apparently is chiefly through the effect of the drugs on the glomeruli (purines) and tubules (mercury derivatives) of the kidneys, whether the drugs act also through some process that controls the water content of the tissues themselves is not known

D **Other drug therapy** Although drug therapy other than that directed toward rest and stimulation of the heart by digitalis and allied drugs and that concerned with diuresis has only a secondary place in congestive heart failure important effects are occasionally secured which mean the difference between success and failure in a given case

1 The *narcotics sedatives and hypnotics* are the most important of these other drugs For acute paroxysmal dyspnea (pulmonary edema) with or without cardiac asthma morphine sulfate 0 015 gm (¼ gr) subcutaneously at the onset of the attack has a striking effect to quiet the patient improve the breathing and shorten the attack Also at times a dose of morphine given to a greatly distressed patient with congestive failure who has been unable to sleep and has been uncomfortable for days may bring the first rest and peace of mind and start the patient on the road to recovery morphinism should of course be avoided by omitting the drug as soon as possible Atropine sulfate 0 6 mg (1/100 gr) may be given with the morphine to reduce the nausea from its vagal effect as well as to reduce secretions Pantopon in the dosage of 0 02 gm (⅓ gr) or Dilaudid 0 002 gm (1/32 gr) may be tolerated better and have as effective therapeutic action as morphine in some patients Even codeine sulfate may on occasion be used effectively in the dosage of 0 03 to 0 06 gm (½ to 1 gr) subcutaneously or by mouth in the place of morphine which has more disagreeable after-effects Bromides whisky or brandy and the hypnotics (of many kinds) also have a place in certain cases bothered by headache worry and sleeplessness Narcotics should be generally omitted when there is distressing Cheyne Stokes respiration When phenobarbital and allied hypnotics are ineffective or actually disturbing in their action and morphine is not applicable a very useful and safe drug to control insomnia and great restlessness is paraldehyde given by mouth rectum or intramuscularly in the dosage of 8 to 16 cc (2 to 4 drachms) to be repeated as needed

2 *Oxygen inhalation* (50 to 100 per cent oxygen by special mask or in special tent or chamber or by naso- or oropharyngeal insufflation) has an important place in combating dyspnea and cyanosis in acute congestive failure

and in tiding cardiac patients over important complications especially pul monary infection and infarction and although not suitable for constant use in chronic failure it may be helpful in daily rations in the case of patients with persistent congestion of the lungs The introduction of the gas helium in the place of air as the diluent of the oxygen helped very materially in reducing respiratory effort in the inhalation of oxygen (Barach 1934) but helium leaks easily and has been expensive and difficult to obtain especially in wartime

3 In many cases of congestive heart failure or very limited myocardial reserve in which the diet is inadequate or absorption of food elements defective sometimes because of the disease itself and sometimes because of the effect of drugs it is essential to administer *vitamins* Such therapy in milder cases may be by mouth in the form of (a) vitamin B complex which contains thiamine nicotinic acid and riboflavin in amounts sufficient to combat beriberi pellagra and dermatoses (b) orange juice to combat scurvy and when necessary (c) vitamins A and D In severe cases with evident avitaminosis usually multiple it may be necessary to give vitamins parenterally for example thiamine HCl 50 to 100 mg daily nicotinic acid 50 to 80 mg and ascorbic acid 50 to 150 mg or more if needed urgently for actual scurvy (up to 1 200 mg in the first dose)

4 The *cathartics and laxatives* are often indispensable Half an ounce of magnesium sulfate every day or every other day may yield one or two watery stools which help not only to keep the bowels open but to get rid of edema Other cathartics may also be used avoiding those containing sodium Senna in the form of a simple aqueous extract of the pods is often a mild but effective laxative Vigorous purgation is to be strongly deprecated because of its weaken ing effect which is in part due to the repeated need of going to stool when absolute rest would be far better for the patient and in part du to the nausea that may be induced

5 *The drug treatment of other diseases* like syphilis which complicate congestive heart failure must be carried out with the greatest of care if at all Generally it is wise to omit all such treatment until the heart has regained its strength

6 Symptomatic treatment of headache indigestion and other functional disorders may be carried out as in the absence of heart failure except that drugs containing sodium should not be given except in very small dosage Various other preparations that have been given in the past for supposedly specific myocardial action like dextrose (glucose) intravenously have been largely abandoned

E **Diet, salt and fluid intake** *Diet regulation* is an important part of the treatment of congestive failure Much has been written on this subject in the past but practically all the information afforded has been empirical based on personal or vague opinions about specific foods and fluid intake General advice has been given to restrict the diet to simple food relatively light in caloric value and in bulk with some restriction of fluids and salt Although this advice has been effective for generations in the case of individuals with heart disease without severe involvement in the form of myocardial or coronary insufficiency many cases have needed better detailed advice Fortunately

during the last five to ten years such advice has come and although we are not yet at the end of the story we can be much more specific and helpful especially in the case of myocardial insufficiency and congestive heart failure

In the first place the most important item of all is the *restriction of sodium* to a reasonably low level sometimes to an extremely low level temporarily to help clear congestion The specific value of the restriction of sodium chloride in the control of congestion was first clearly pointed out by Widal and Lemierre in 1903 and by Strauss in 1908 * It is the sodium that holds water in the body and hence the less sodium intake or the greater the sodium output the less water is held in the body with less congestion and the more comfortable is the patient There is a limit to sodium restriction however and sometimes there are unfortunate results in the form of salt lack Therefore it is possible to overdo this very helpful therapy of limited salt intake

Salt that is sodium chloride should be fairly accurately measured in the food and there are tables now listing the sodium content of many foods The reader is referred to one special list as follows Sodium and Potassium Analyses of Foods and Waters Fifth List October 1947 With Additions and Corrections Mead Johnson & Company Evansville 21 Indiana The sodium chloride content of the usual diet varies greatly according to individual liking and habit There is a range from about 5 to 15 or more grams per day 8 to 10 being very common A simple reduction to 3 or 4 gm a day may suffice to help keep congestion under control Sometimes however a stricter reduction is necessary to 1 or 2 gm a day and on occasion a stricter reduction is to less than 1 gm which would give an actual sodium level of less than ½ gm Such is found in certain diets like the rice diet of Kempner Control testing of the amount of sodium taken in can be gauged by the measurement of the chlorides in the urine Strict sodium restriction can be carried out for a good many weeks or months and in less severe form for years but there should be frequent appraisal of the details of the diet in each case Various salt substitutes have been introduced to make more palatable the low sodium diets unfortunately the best containing lithium chloride was used too freely and resulted in lithium poisoning in some cases but in small dosage (a few drops at each meal) it may still be taken to advantage

An ingenious method for limiting the sodium content of the body has been the administration of resinous compounds which attract and hold electrolytes in particular sodium in the gastrointestinal contents (too great a depletion of other electrolytes especially of potassium is avoided) various preparations of resin although not yet perfected and difficult for some patients to take have permitted the ingestion of more palatable food and longer time intervals between mercurial injections in suitable cases of obstinate congestive heart failure (Dock 1946 1950)

The next important item about the food and fluids concerns the caloric

* It is of interest that John of Gaddesden in his famous book (*Rosa anglica practica medicinae a capite ad pedes* printed by Johannes Antonius Birreta Pavia 149-) refers to the value of limiting the salt content of the diet in cases of dropsy His work was in manuscript at the time of Chaucer in the middle of the fourteenth century six hundred years ago

value This should be adequate to maintain nutrition and yet low enough to allow loss of weight if there is obesity Sometimes four or five small meals a day are more readily tolerated than two or three larger ones especially in the case of a severely ill patient Not infrequently the old Karell diet (cure de lait) can be used for a day or two with benefit This consists of 800 cc of skimmed milk divided into four portions during twenty four hours This is a starvation diet with restriction of salt and limitation of metabolic needs for digestion which may help to start treatment in the case of a severely congested patient It is not to be used as a rule for more than a day or two at a time In some diets such as that of the rice diet the protein intake is very low This is generally not necessary It is usually best to give protein intake enough to keep a normal nitrogen balance—1 gm per kilogram of body weight is usually satisfactory If there is much loss of albumin by the urine in the complicated case, more protein may be added to the food It is generally best to keep all fats low and to supply most of the calories by carbohydrates

Finally as to fluid intake formerly and for centuries as a matter of fact there was great restriction of fluid intake with unhappy results The patient was often rendered very miserable and constantly thirsty by the reduction of fluids to one liter or less in twenty four hours Now we have come to realize belatedly that adequate fluids should be administered usually best in the amount of about 2 to 3 liters in twenty four hours and in rare cases even more if the kidney status demands such for adequate ridding of the blood of impurities Only infrequently is it necessary to force fluids Most patients do well with fluid intake varying from 1½ to 2½ or 3 liters

In order adequately to control the fluid intake charts of 24 hour intake and output should be carefully kept during the period of congestive failure and for a few weeks thereafter, also so far as possible a daily weight chart should be kept for often the very first indication of the onset or recurrence of edema is an otherwise unexplained rapid gain in weight

Vitamins (see page 840) and adequate protein (a minimum of 1 gm per kilogram daily for average sized adults amounting to 60 to 70 gm in 24 hours) should be carefully included in the diet in order to maintain as good general health as possible and to prevent complications of avitaminosis and hypoproteinemia which may themselves cause heart trouble and edema although such complications are not as a rule at all prominent and in severe degree are uncommon yet they may on occasion be a cause for obstinate edema

F **Various mechanical therapeutic measures** 1 *Venesection* is rarely necessary in the treatment of congestive heart failure, but sometimes as an emergency measure it gives relief and saves lives It was much more often necessary in the days before there was a proper appreciation of how to give digitalis, that is before the time of more or less universal digitalization and maintenance of digitalis effect and also before adequate mercurial diuresis and restriction of sodium intake Venesection is applicable to two types of patients first and chiefly the cardiac patient with acute and fulminating congestive failure as in cases of pulmonary edema and of marked venous congestion, and second

rarely the chronic plethoric non nephritic hypertensive cardiac patient who tends to have obstinate or readily recurrent edema and persistently high venous pressure (over 20 cm of water in arm vein) in spite of rest digitalis diuretics and other therapy Blood should be removed from arm vein by knife or needle in amounts between 250 and 500 cc (½ to 1 pt) The procedure may be repeated if needed but it should not be done unless the venous pressure is elevated and it should not be the first treatment of choice

Another way by which temporarily the heart may be relieved of excess blood especially helpful in acute failure with pulmonary edema is constriction of the proximal parts of three extremities at a time by blood pressure cuffs or similar bands cutting off temporarily the venous circulation and so sidetracking much blood Each extremity should be released in turn for fifteen minutes at a time This procedure should however be used as little as possible because of the hazard of causing phlebothrombosis in the legs with resulting pulmonary embolism

2 When rest digitalis diuretics and other measures fail to relieve ascites or hydrothorax and oppression from the fluid is disagreeable *paracentesis* should be done and as much fluid as possible withdrawn from peritoneal or pleural cavities without exhausting the patient This is especially important in the case of hydrothorax because of the greater embarrassment of the already difficult breathing by the reduction of the vital capacity by the pleural fluid and because fluid is absorbed more slowly from the pleural than from the peritoneal cavity It is best to use local anesthesia with 0 5 to 1 per cent procaine (novocaine) before the trocar is inserted

3 For obstinate massive edema of the legs a condition far less common than a decade or two ago an incision 3 in long in the dorsum of each foot or multiple punctures of the skin of each calf may be made to drain off as much fluid as possible aseptically into dressings or sterile jars or pans but a method much to be preferred is the use of *Southey s tubes* (Southey 1877) small cannulas which may be inserted into the feet or legs by means of trocars two or three on each side with rubber tubes to carry off the edema fluid which can thus be measured (Figure 150 page 820) Curschmann s tubes are less desirable than Southey s tubes in the treatment of obstinate edema because of their larger size It is best to have the patient in the sitting position preferably in a special chair bed to get the full benefit from this procedure Sometimes enormous quantities of fluid can be drained off by the Southey s tubes even as much as 6 liters in twenty four hours or 15 liters (about 30 pounds) in three or four days Painful massive edema of the scrotum which is not relieved by the insertion of the Southey s tubes in the legs may be largely removed by putting one of the tubes directly into the scrotum itself as much as a liter of fluid can be drained from the scrotum in this way in a day or two The utilization of these mechanical drainage measures is best reserved however for cases of obstinate edema which are not relieved in other ways Infection in such patients can be prevented by the use of penicillin parenterally while the tubes are in use As indicated above the need of such treatment has been

steadily growing rarer with improvement of our other therapeutic measures cardiac patients still fail and die but as a rule they die dry—we no longer see much anasarca today

4 The method of treatment a type of cardiolysis in reality a *thoracolysis* or *rib resection (precordial thoracectomy)* designed to afford mechanical relief to an embarrassed circulation in which heart failure is threatened or has actually begun which was mentioned in previous editions of this book has been rarely carried out so far as I am aware It is similar to the equally rare operative procedure introduced to give relief to the heart when it is tied to the chest wall by pericardial adhesions (Brauer s operation Brauer 1902) Several ribs and costal cartilages usually the fourth fifth and sixth of the left anterior chest wall are removed in this operation in order to give more freedom to a very large heart pounding against a rather rigid barrier The operation was apparently beneficial in a few cases chiefly by relief of subjective discomfort (palpitation and precordial ache), but it must still be considered as an experimental measure and not likely to be helpful in many cases It has been developed further in the last fourteen years since the publication of the second edition of this book but it must be realized that there results from this procedure an undesirable deformity of the thorax interfering with the mechanism of respiration

5 *Total thyroidectomy* in the treatment of congestive heart failure and angina pectoris was an extremely interesting innovation years ago (Blumgart Levine and Berlin 1933) It had been observed that a cardiac patient thought to have thyroid disease improved considerably for a period of time after the subtotal removal of a normal thyroid gland this was the forerunner of the idea that was finally put into execution that total ablation might dissipate congestive heart failure and angina pectoris by its effect in reducing markedly the basal metabolic rate and so cutting down the demands on the myocardium and coronary circulation This idea proved true and the operation became for a few years established as one of the radical measures of cardiac treatment that seemed suitable in about 1 per cent of the patients routinely seen for congestive failure or angina pectoris Both successes and failures were reported in the application of this treatment Almost all of the early enthusiasm has waned and yet there remained a place for this idea and recently it has evolved into a medical thyroidectomy for obstinate myocardial or coronary insufficiency by the ingenious use of irradiated iodine I 131 (Blumgart and Freedberg 1948) Minute amounts of this preparation are given by mouth over a period of 2 or 3 weeks in order to introduce from 25 to 100 millicuries into the body a considerable proportion of which settles in the thyroid gland where the cells are exposed to the radiation In the course of 4 to 8 weeks the metabolic rate is reduced sufficiently to afford relief of symptoms in most cases A high degree of myxedema is prevented by the administration of small doses of thyroid

Other surgical operations such as appendectomy to correct serious lesions in the presence of congestive heart failure should be limited to emergencies and so far as possible some preparation by rapid digitalization should be

carried out first if there is inadequate digitalis therapy already Thyroidectomy for thyrotoxicosis is however one operation which is as a rule indicated rather than contraindicated This surgical measure may actually abolish the congestive heart failure In cases of prostatic obstruction also it may be difficult to restore or to hold myocardial competency until the patient has been put on constant bladder drainage and submitted later to a transurethral prostatectomy In any of these surgical procedures the greatest care must be taken in securing the best anesthesia possible (see Chapter 23)

6 *Physical therapy* Special measures of physical therapy—exercises massage baths electrotherapy—have little place in the treatment of congestive failure except for massage of arms and legs which may be useful in helping to maintain the peripheral circulation and so to prevent phlebothrombosis the precursor of pulmonary embolism and gentle passive or active exercises during convalescence but not while there is still dyspnea or edema Other measures such as carbon dioxide baths and more vigorous exercises are to be prescribed only after the congestive failure has cleared up to help to improve the general circulation and thereby to increase the cardiac reserve

G **Environment and other factors** Finally it is important to remember that a patient may be overtreated and hastened to his end by the too zealous simultaneous application of a number of measures each one of which may be valuable in itself when applied with common sense A patient who at home is in a chronic state of slight to moderate but not dangerous congestive failure may be brought for treatment to a hospital where in a new and strange environment he is bled purged much restricted as to food and fluids and given a number of potent drugs Unable to stand the strain of so much effective therapy he may die within a few days *Good judgment* must be well mixed with all the rest of the treatment of such a sick patient as the one with congestive heart failure Health resorts a long way from the patient s home are far less suitable for his care during severe congestive failure than are hospitals near at hand or the patient s own home itself During convalescence the change of scene and divers interests at some well-conducted sanitarium or spa may justify the patient s journey thither but good medical supervision should be a requisite the patient should not return home a wreck as has sometimes happened Also during convalescence it is worthwhile to prescribe not only graded exercise but some interest like music art science history literature or even stamp collecting as well Last but not least is the *spirit of cheerfulness* that should surround the patient a natural attribute of a good doctor and a good nurse and one of the chief elements in the psychotherapy of heart disease

Differential diagnosis Congestive heart failure must be differentiated from neurocirculatory asthenia from the effect of obesity and poor physical training on the respiratory reserve and from nephritis starvation peritonitis cirrhosis of the liver malignant disease constrictive pericarditis (acute or chronic) and infections which may cause edema ascites hepatic enlargement, hydrothorax and rales in the lungs The diagnosis of congestive heart failure is generally readily made by finding the combination of serious organic

heart disease dyspnea or dependent edema and a favorable response to digitalis therapy It is particularly important on rare occasions to distinguish acute pulmonary edema due to left ventricular failure or to mitral stenosis from that of so called neurogenic origin (see page 63 Chapter 4)

There are two conditions that are particularly likely to be confused with the results of myocardial failure one very common namely *pulmonary disease* and the other rare acute or chronic *constrictive pericarditis* Careful history and physical examination as a rule prevent errors Pulmonary symptoms and signs are not due to heart disease unless there is evidence of that disease in the form of cardiac enlargement murmurs of valvular deformity or important myocardial infarction the main difficulty is in determining the relative responsibility in producing symptoms and signs when both heart disease and pulmonary disease are present in the same patient Acute or chronic constrictive pericarditis causes all the evidences of congestion in the systemic veins liver and dependent parts of the body that are caused by myocardial failure but the heart itself is usually but little involved in the case of constrictive pericarditis except for a rather characteristic electrocardiogram and sometimes a slightly enlarged x ray heart shadow, and there is a history usually in a young person of the gradual development of dropsy especially a big liver and ascites without adequate heart trouble to account for it and unaided by digitalis therapy in a few cases an acute pericarditis precedes the chronic trouble (see Chapter 27)

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CHAPTER 31

DISORDERS OF VASCULAR FUNCTION INCLUDING GENERAL VASCULAR FAILURE (SHOCK) AND RAYNAUD'S DISEASE

An essential factor in the maintenance of the circulation of the blood is the proper functioning of the arterioles and venules Disorders of vascular function comprise an important example of the failure of adaptation of the human organism and can have important consequences They are of two main types (1) general vascular disorders which are likely to be serious and (2) local involvement of the peripheral circulation as in Raynaud s disease with little or no influence on the heart itself or on the health as a whole although at times causing great discomfort These types together constitute a section of the field of normal and abnormal cardiovascular physiology which is becoming better understood and more clearly defined but which is still in need of further exploration As stated in the last edition of this book neither exact knowledge of the mechanism of these vascular disorders nor their therapy has as yet reached a stage comparable to that of the understanding of disorders of function of the heart itself Although it is certain that knowledge of vascular disorders will gain many additions in the future as it had indeed already done during the last generation it is not likely that this chapter will ever become the most important part of a survey of cardiovascular disease as a whole as has sometimes been intimated The heart perforce remains the most vital part of the circulatory apparatus

Functional vascular disorders consist of an abnormal degree of distribution of vasoconstriction and vasodilatation and of an abnormal permeability of the walls of the smallest blood vessels There may be an abnormal degree of vasoconstriction in one part of the body coexistent with abnormal vasodilatation in another part Just how much the two opposite conditions of vasoconstriction and vasodilatation may be due to local vascular irritability how much to the direct effect of toxins on the vessel walls and how much to nervous stimulation central and peripheral still remains in many cases difficult or impossible to say

GENERAL OR EXTENSIVE DISORDERS OF VASCULAR FUNCTION

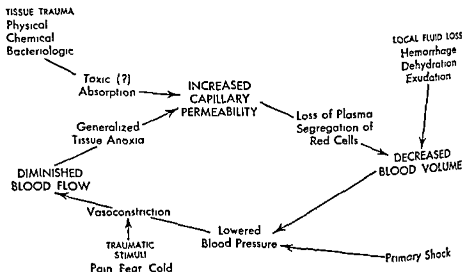
Vasoconstriction Experimentally general vasoconstriction can be produced by the action of certain drugs especially epinephrine (adrenaline) and Pituitrin by direct electric stimulation of the sympathetic nerves and by indirect sympathetic stimulation by fear excitement cold and the toxic condition that causes a shaking chill

Clinically there is reason to believe that general vasoconstriction by increasing the resistance to the circulation of blood is responsible for *essential hypertension* or *hyperpiesia* If such a mechanism exists as seems likely it yet remains to be discovered whether the vasoconstriction is always due directly to some renal metabolic or extraneous toxin in the blood stream to sympathetic nerve effect from central stimulation or to local irritability of unknown cause widespread throughout the vascular tree A crystalline pressor substance called angiotonin or hypertensin has been isolated in recent years from the reaction of a renal extract (renin) and renin activator (Houssay Fasciolo and Taquini 1938 Page et al 1940) Latterly tests of vasomotor lability have been introduced to determine the degree to which generalized vasoconstriction can be influenced and thus judged as to possible amenability to sedative or dilatation therapy or to sympathectomy and also perhaps in picking out potential hypertensive cases These have been called the cold pressor test and the sedation test They consist of noting the effect on the blood pressure of immersing one hand for one minute in ice cold water (normally except in very sensitive persons the blood pressure should not rise over 15 mm mercury systolic—Hines and Brown 1933) and of recording the low levels to which systolic and diastolic blood pressures drop hourly for 12 hours after the administration of 0 2 gm (3 gr) of Sodium Amytal bv mouth each time at 7 8 and 9 o clock in the evening (see Chapter 19)

Vasodilatation Experimentally general vasodilatation can be produced by various poisons and by sympathetic nerve depression Certain sensitive individuals are more prone to such vasomotor disturbances than are others and the same person will react differently at different times Now and than an otherwise healthy young person will faint under the stress of some simple procedure such as the taking of the blood pressure or standing at attention Also the simple pooling of blood in varicose veins may cause dizziness and other symptoms Extensive vasodilatation may be preceded by a short interval of vasoconstriction

Vascular shock or failure General peripheral circulatory failure is a serious state characterized by progressive loss of circulating blood volume due to generalized increase in capillary permeability Two explanations have been advanced to account for this widespread change in capillary permeability first that it results through the action of some toxic factor absorbed from the area of injury and second that the increase in capillary permeability is caused by the tissue anoxia which results from reduced circulation (Freeman 1942)

Accident hemorrhage severe toxemia great pain and extreme fatigue are all factors which may produce this syndrome of prostration faintness hypotension sometimes coma marked prolongation of the circulation time and in surgical traumatic and hemorrhagic shock diminished blood volume An important secondary infection in the traumatized tissues has been shown to be a cause for a prolonged state of shock (Aub et al 1944 Prinzmetal et al 1944) but the prophylactic use of penicillin and other specific measures should protect against this factor in the future A compensatory but unavailing vasoconstriction may be brought into play The following diagram (Freeman 1942) illustrates the various relationships in vascular shock, which is a process with vicious circle rather than a static condition



THE PROCESS OF SHOCK

Treatment of milder examples of vascular shock such as syncope is simple The recumbent position rest inhalation of the fumes of smelling salts (an aromatic preparation of ammonium carbonate) a teaspoonful of aromatic spirits of ammonia in a little water a sip of brandy and a drink of strong hot coffee are all useful procedures in treating faintness of this sort Strychnine sulfate given subcutaneously in large doses (1 to 3 mg 1/60 to 1/20 gr) is thought by some observers to have a favorable effect

For the more severe cases of surgical shock as after severe accident or hemorrhage the treatment is as yet often unsatisfactory *The immediate increase of the volume of the circulating blood best by transfusion is the measure of therapy par excellence* the increase of circulating blood volume by infusion or transfusion is often lifesaving It is best to give whole blood for hemorrhage and plasma when there is fluid loss into the tissues in other states of shock *Most important of all is the fact that this kind of therapy is far more valuable in prevention when shock threatens than in treatment*

Drugs The administration of caffeine in large dosage by mouth subcutaneously or intravenously (10 to 15 gr of caffeine sodiobenzoate) at intervals of three or four hours is only palliative though it may help Epinephrine (adrenaline) hydrochloride injected intravenously or intramuscularly in the dose of 0 5 to 1 cc of a 1 1000 solution and Pituitrin (or the derivative Pitressin containing the active pressor principle with little or none of the oxytocic principle which causes uterine contractions and is used in obstetrics) injected intramuscularly or subcutaneously in the dose of 0 5 to 1 cc (equivalent to 0 1 to 0 2 gr of the posterior lobe of the pituitary gland) have also been recommended for use in shock but their action is uncertain and likely to be followed by unfavorable after-effects such as increase in the vasodilatation after the transient vasoconstriction or a primary vasodilatation itself The difficulty with epinephrine and Pituitrin is that they act on the arterioles whereas the fault lies in the lack of tone in capillaries and venules Cortical extract has been tried with apparent benefit as a prophylactic against experimental shock in animals and surgical shock in man (Helfrich Cassels and Cole 1942) but its beneficial effect has not been confirmed Drugs such as digitalis and strophanthin directed at the heart itself have proved of no avail and may do harm The heart in such cases is struggling with an inadequate supply of blood and needs no direct stimulation for itself *it should not be slowed*

Of late years it has been agreed that *circulatory failure caused by acute infections* should be separated as to findings and treatment from that of hemorrhagic or traumatic shock Ebert and Stead (1941) found in cases of lobar pneumonia with bacteriemia and of streptococcal and staphylococcal septicemia with circulatory failure characterized by a decrease in peripheral blood flow and a fall in arterial pressure that measurements of the hematocrit level serum protein concentration and plasma volume showed no significant hemoconcentration or diminished blood volume that the venous pressure was normal and that elevating the foot of the bed and transfusing with whole blood did not produce any improvement in the circulation They concluded that the entire cardiovascular system was depressed or damaged by the infection with simultaneous injury to the heart and loss of venous tone and that therapy must be directed toward overcoming the infection rather than attempting to treat the circulatory failure per se It may be that shock associated with the acute infections differs from traumatic shock in large part only in the persistence of the exciting factor and not so much in a cardiac factor—which illustrates the need of more light on all the types and mechanisms of what we now call circulatory failure

The shock syndrome produced by acute myocardial infarction or acute congestive heart failure may need to be differentiated from the circulatory failure secondary to hemorrhage accident operation or infection When along with signs of diminished peripheral blood flow there is congestion of the pulmonary or of the systemic venous bed the clinical picture of shock is often to be ascribed rather to the heart failure than to an inadequate venous

return of blood to the heart resulting from decrease in blood volume or pooling of blood in the peripheral circulation (Stead and Ebert 1942) There are however cases in which doubtless both factors are responsible primarily acute coronary occlusion or acute congestive heart failure and secondarily vascular failure

LOCAL DISORDERS OF VASCULAR FUNCTION

Vasoconstriction Experimentally and physiologically vasoconstriction of a single artery or of a group of arteries can be easily induced by direct irritation by the application of cold and toxic agents to the vessel itself or to the skin over the superficial arteries involved or by the stimulation of the sympathetic nerves controlling the vessels

Vascular crises Clinically there are a few abnormal states which are undoubtedly dependent on local vasoconstriction One of these is the so-called vascular crisis or spasm involving cerebral retinal coronary or other arteries supplying such vital tissue that important symptoms are quickly produced if the blood supply to this tissue is cut off (Pal, 1905) Transient dizziness syncope paralyses tinnitus and visual disturbances lasting a few seconds to a few minutes have been commonly reported and thought to be due to local vasoconstriction of somewhat abnormal and irritable vessels such vascular crises occur for the most part in persons over fifty years of age who have hyperpiesia It is often difficult to rule out in such cases slight lesions—hemorrhagic embolic or thrombotic in nature—but it is quite certain that vascular crises do occur Retinal arterial spasm has actually been observed and recently it has been proved experimentally that the cerebral arteries are under sympathetic nerve control Although intermittent claudication (pain in the calves on walking) may in some instances be due to vascular crises it is more likely that permanent arterial narrowing is responsible there the circulation being adequate when the muscles are at rest nevertheless the benefit that sometimes results in these cases from lumbar sympathectomy or procaine injection indicates that there may well be a considerable superimposed vasoconstriction (Freeman and Montgomery 1942) It is possible that vascular crises (coronary spasms) are at times a factor in the production of angina pectoris When there is a general vasoconstricting storm producing paroxysmal hypertension with or without angina pectoris the condition has been called *Nothnagel s syndrome* (Nothnagel 1867) This should not include paroxysmal hypertension due to a pheochromocytoma Also in recent years Pickering (1948) has shown that much of the so called cerebral vascular spasms constituting a major part of hypertensive encephalopathy is in reality a succession of cerebral vascular accidents (hemorrhage or thrombosis) leaving minute scars of infarction behind them

Raynaud s disease is a spasmodic vasoconstriction of unknown cause affecting the extremities usually both hands often preponderantly either right or left and rarely the feet It causes blanching of the skin a decrease in pulse and symptoms of pain and numbness The syndrome recurs periodically at

longer or shorter intervals (days weeks or months) lasts a few minutes to a few hours at a time and is induced especially by exposure to cold and to nervous excitement when severe trophic disturbances appear and even gangrene may result (Raynaud 1862) In the late stages the arteries themselves become structurally diseased with thickened walls and narrowed lumina and in some cases of Raynaud s disease similar changes have been found in the small vessels of the lungs with extensive pulmonary fibrosis (Linenthal 1942)

Raynaud M *De lasphyxie locale et de la gangrene symetrique des extremites* Thesis Rignoux Paris 1862

The following passages from this pioneer work are of interest (Translation by myself)

From the Preface

'To describe a new disease and above all to give a new name to a group of symptoms which have been long observed and described is a matter certainly less difficult than to associate several apparently different affections under a common law which controls them

Moreover in spite of the title which I have given to this thesis I wish to state at the outset that I have no aspiration to the empty and dangerous honor of pathological innovation Facts are always but facts and there is advantage only in grouping them in orderly arrangement

From Chapter I page 17

I propose to demonstrate that there exists a variety of dry gangrene affecting the extremities which cannot be explained by vascular obliteration a variety characterized especialy by a remarkable tendency to symmetry to such a degree that it always affects similar parts the arms or legs or all four extremities at one time and even in certain cases the nose and ears also I shall try to prove that this kind of gangrene has its origin in a defective innervation of the capillary vessels which will remain for me to describe

As one can see this is a very restricted corner of the general subject of gangrene which I am now undertaking to discuss

From Chapter III page 109

II In order to arrange more satisfactorily the symptomatology and to avoid confusing very different conditions because of their serious nature I shall describe separately local syncope and asphyxia on the one hand and symmetrical gangrene of the extremities on the other

In its simplest form local syncope is a condition perfectly compatible with good health Individuals who have this trouble and who are usually women notice that under the slightest influence sometimes without any appreciable cause one or more of their fingers grow suddenly pale and cold In many cases it is always the same finger that is first affected the others become deadened successively always in the same ord r This phenomenon is known under the name of doigt mort (dead finger) The attack is painless and lasts from a few minutes to several hours The provoking cause is often the feeling of cold what happens ordinarily only under the influence of the most severe cold occurs in the subjects of whom we are now speaking as the result of the slightest drop in temperature sometimes

a simple emotional disturbance is sufficient to produce this effect It appears that the same cause which acts on the capillaries of the face and produces a blush can under the circumstances exert its action especially on the capillaries of the extremities

'The skin of the affected parts assumes a dull white or at times a sallow shade it appears completely exsanguinated The cutaneous sensibility diminishes and then disappears the fingers become like strangers to their owners Their temperature drops notably The attack is followed by a reaction which is often very painful and which gives rise to a sensation quite like that of a numbing cold in the fingers In cases more pronounced especially in those with predominant asphyxia the discoloration of the extremities is replaced by a cyanotic tint of various shades

Page 129 Ætiology VIII A Predisposing causes

Sex This influence is very pronounced in favour of the female sex Of my 25 cases 20 were in women and only 5 in men

Age The influence of age is no less important and to such a degree that one would be almost tempted to reserve for the condition the name juvenile gangrene In the great majority of cases the malady appears between the ages of 18 and 30 years the average of 25 years constituting a time of marked predisposition

Temperament constitution previous illnesses Although all temperaments are subject to this malady individuals of lymphatic and nervous nature are particularly prone

Evidence has been published (Lewis 1929) to indicate that for some unknown reason the palmar arteries are unusually irritable in themselves in Raynaud s disease but other evidence still supports Raynaud s original contention that there is also an important nervous element in the pathogenesis of this disease (White J C 1932) Sympathetic ganglionectomy has been carried out in the treatment of Raynaud s disease with definite relief (Adson and Brown 1929 Mayo and Adson 1932) It has been reported (Agate 1949) that a high percentage of workers who polish metal castings with rotary tools *show intermittent pallor of their hands*

A form of diffuse scleroderma has been found by Lewis and Landis (1931) to be due to a vascular defect similar to that noted in some cases of Raynaud s disease

Vasodilatation Vasodilatation is easily induced locally by the application of heat and by traumatic skin lesions Exercise of a muscle increases very much the blood flow through it dilatation of the local arteries and arterioles bringing this about Sympathectomy temporary paralysis of the sympathetic nerve connections by local anesthetic (as with novocaine) and permanent destruction of the sympathetic fibers by the injection of alcohol cause vasodilatation of the blood vessels in the part of the body affected and these measures have been employed in the treatment of trophic disorders and of pain which may result from abnormal vasoconstriction

Blushing is a common phenomenon due to local effects on the peripheral arterioles especially in the face from nervous excitement

Chronic dilatation of the blood vessels in certain parts of the body *telangectasis* (τέλος end ἀγγεῖον vessel and ἔκτασις development) especially in the face may follow alcoholism or constant or repeated exposure to the atmosphere of raw climates it is frequently also a congenital defect

There are two other local pathologic skin conditions dependent mainly on abnormal vasodilatation These are the common *chilblain*—an acute painful or itching reddened area of skin usually of hand or foot—due to prolonged exposure to cold and wet especially in sensitive individuals and the rare *erythromelalgia* (ἐρυθρός red μέλο limb and ἄλγος pain) of unknown cause consisting of a paroxysmal abnormal local vasodilatation of the extremities with redness throbbing and pain not usually leading to any trophic disturbance (Weir Mitchell 1878)

Finally the trauma or toxin that causes local or general vasodilatation may set free from the tissues a histamine like substance which acts on the walls of the smaller blood vessels allowing the exudation of fluid into the peri vascular tissues this is most readily seen under the skin in the form of wheals *urticaria* (from the Latin *urtica* nettle) (Lewis and Grant 1924)

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CHAPTER 32

PREMATURE BEATS (EXTRASYSTOLES) PAROXYSMAL TACHYCARDIA

Not much revision has been found necessary in the case of the last three chapters of the book but they have been carefully reviewed to bring them fully up to date

The commonest and simplest abnormalities of cardiac rhythm are premature beats (or extrasystoles) and paroxysmal tachycardia Related in mechanism and often occurring in the same patient they are of but little clinical significance Their frequency and likelihood of overemphasis render them however a subject of some importance

PREMATURE BEATS

Premature contractions of the heart or extrasystoles as they are sometimes called are due to abnormal or re entry stimuli in various parts of the heart atria ventricles atrioventricular bundle and even the nodes themselves A perfectly satisfactory term is difficult to find Premature beat or premature contraction seems most suitable because the chief feature of this abnormality of mechanism is its prematurity on rare occasions, however when it happens that the normal (sinoatrial nodal) pacemaker is depressed and the normal beat delayed there may be an abnormal or ectopic beat which is not premature The term extrasystole in common use is less suitable in that the premature beat is only rarely a true extra or additional systole it merely comes early and replaces the normal systole if extra is taken to mean 'ectopic that is, arising from an abnormal point it is more suitably applied but it is also possible to have a premature beat which arises in or very close to the normal pacemaker

Incidence The premature beat is almost universal Probably only a very rare individual escapes having premature beats at some time of his life although they often pass unnoticed It is without doubt the commonest of all cardiac abnormalities in fact it is so frequent among otherwise normal individuals that it hardly deserves the name of abnormality

Mechanism (abnormal physiology) A wave of excitation and contraction may arise abnormally in the heart spreading from a point outside the limits of the normal pacemaker (sinoatrial node) or rarely from within the normal pacemaker itself (and then called *nomotopic*) The stimulus must occur at a time when the muscle will respond that is when it is not still in the refractory (unresponsive) phase due to the existence of a state of contraction or recovery It is possible that the premature beat may be the result of the re-entry of the previous normal (or abnormal) excitation wave by way of an area of muscle refractory to the direct spread of the wave but recovering sufficiently to allow response a little later to the same excitation wave reaching it slowly in a round-about course

(a) *Atrial premature beat* An abnormal wave starting in the atrial muscle spreads in all directions it not only descends to the atrioventricular junctional tissue thus giving rise to a ventricular response but it also ascends to the sino-atrial node thus discharging a normal impulse already in the process of development, and so interrupting the dominant rhythm The atrial premature beat whose atrial component in the electrocardiogram (*P* wave) is usually inverted is followed by a pause which is equivalent to the time interval needed for its impulse to reach the sinoatrial node plus the usual time interval between two normal sinoatrial contractions This pause plus the time interval between the normal beat just preceding the atrial premature beat and the atrial premature beat itself gives an interval less than that covered by two normal beats hence this pause is not compensatory the spacing of the groups of beats in electrocardiogram and arteriogram is interfered with and the dominant rhythm is disturbed (Figure 154 page 868)

Usually the ventricles respond to an atrial premature beat but often they do so in an abnormal way that is there is a state of intraventricular block or defective conduction in the bundle branches such block is doubtless due to relative degrees of refractoriness (or slowness of recovery from the previous contraction) in various parts of the conducting system The earlier the atrial premature beat the more likely is the ventricular response to be abnormal that is to show intraventricular block Such abnormal response has not been found to be of any clinical significance as it is a more or less normal transient functional condition Rarely the ventricles may fail to respond at all to atrial premature beats this lack of response is not remarkable if the abnormal beat comes very early but it is strongly suggestive of some important degree of atrioventricular block if the premature beat is not very early

(b) *Ventricular premature beat* If an abnormal excitation wave starts in right or left ventricle it spreads in all directions sometimes if it starts very late in diastole it meets the normal wave as it comes down through the junctional tissues from the atria and produces with it a composite contraction a condition comparable to that which may also occur in the atria in the case of atrial premature beats

Usually the premature ventricular wave passes up to the atrioventricular bundle and node but not through it into the atria the normal atrial contr

tion begins at this time and thus occurs simultaneously with the abnormal ventricular contraction The atrioventricular valves being shut as the result of the ventricular premature beat the blood is deflected back from the atria by the normal atrial contraction into the great veins Since the premature ventricular contraction does not as a rule disturb the normal regular sequence of atrial waves it is followed by a pause which is called compensatory and the

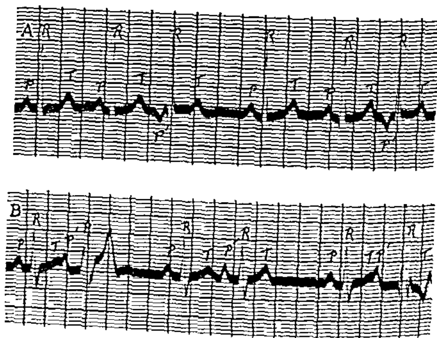


FIG 154 Electrocardiograms (Lead 2) showing atrial premature beats (A) Inverted *P* waves with normal ventricular response (*B*) upright but premature *P* waves with abnormal (aberrant) ventricular response varying in degree according to the prematurity of the *P* waves

dominant rhythm is not disturbed The interval between the normal heart beat just preceding the premature beat and the ventricular premature beat itself added to the compensatory pause between the ventricular premature beat and the next normal beat gives an interval just equal to that covered by two normal beats when sinus arrhythmia is not present to interfere seriously with the measurements (Figure 155)

Sometimes the ventricular premature beat sends its impulse back through the atrioventricular bundle and node to cause a retrograde atrial contraction it does then interfere with the dominant sinoatrial rhythm just as an atrial premature beat also interferes with such rhythm When this happens the pause following the ventricular premature beat is not compensatory The electrocardiograms of ventricular premature beats are usually bizarre so far as shape of the *QRS* and *T* waves are concerned due to the abnormal spread of the impulse resembling somewhat that in bundle branch block When the impulse has

its origin clearly in the left ventricle and spreads up and to the right the *QRS* wave in Lead 1 is wide and chiefly inverted with high *T* wave and is rather similar to the *QRS* wave seen in normal rhythm with right bundle branch block when it rises clearly in the right ventricle the *QRS* is wide and upwardly directed in Lead 1 with deep *T* resembling the *QRS* seen in normal rhythm with left bundle branch block the *QRS* and *T* waves in Lead 3 are almost

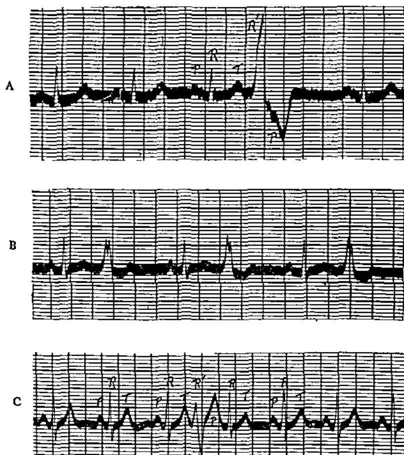


FIG 155 Electrocardiograms (Lead 2) showing ventricular premature beats (*A*) followed by compensatory pause (*B*) occurring every other beat to produce a bigeminal pulse and (*C*) interpolated

always oppositely directed to those in Lead 1 The precordial leads may pick out the origin of the premature beats quickly both by the short interval before the intrinsic deflection and by the upright direction of the complex over the ventricle involved

The separation of right and left ventricular premature beats is of little or no clinical significance

Finally the ventricular premature beat may come so early or the preceding heart rate may be so slow, that the ventricular tissue is no longer refractory when the next normal sinoatrial impulse reaches the junctional tissue the ventricle then responds again in rather quick succession but usually with some delay due to partial atrioventricular block, and with relatively small pressure because of the small amount of blood left in the heart Such a mechanism is called interpolation of a ventricular premature beat (*interpolated ventricular premature beat*) and is an example of a true extra or additional systole (Figure 155C)

(c) *Atrioventricular nodal premature beat* A premature beat arising in the atrioventricular node or bundle and causing simultaneous contraction of atria and ventricles has an effect like a ventricular premature beat with retrograde atrial contraction and disturbs the dominant rhythm just as does an atrial premature beat It is however a rare type

(d) *Sinoatrial nodal (nomotopic) premature beat* A premature beat may also arise rarely in or close to the sinoatrial node (nomotopic) such a beat acts like an atrial premature beat followed by a relatively short pause which is in fact just the length of an interval between normal beats

Parasystole The subject of the mechanism of premature beats should not be left without mention of the interesting theory of parasystole which helps to explain the regular occurrence of repeated premature beats in certain cases It is proposed that a new and abnormal pacemaker is constantly building up stimuli just as is the normal sinoatrial nodal pacemaker but at a different rate When the refractory state of the muscle and local block about the abnormal pacemaker do not interfere the impulse from the new pacemaker gives rise to premature beats in a regular or irregular relationship to the normal beats The relative rates of the independent rhythms in parasystole can be worked out by careful measurements of the tracings Whether or not the impulse production in such abnormal pacemaker may be of the character of a circus wave is not known

Etiology *Cause* The cause of a premature beat is an abnormal stimulus production or course in the heart muscle Certain factors are sometimes responsible for such an abnormal mechanism but the manner of their working is obscure Direct electrical mechanical or chemical stimulation of an experimental animal s heart will produce premature beats if the stimulation is of sufficient strength that is if it surpasses a certain threshold of responsiveness Nerve stimulation may also induce premature beats

In man premature beats have been induced by mechanical stimulation (tapping) of the heart exposed either during operation for some thoracic condition or in very rare cases exposed congenitally Electrically induced premature beats have also been reported in the case of a man with heart bared during drainage of a purulent pericarditis (Barker Macleod and Alexander 1930) Vagus nerve stimulation by carotid pressure in the neck or reflexly by sudden pain anywhere in the body has occasionally elicited premature beats Forced respiration breath holding overexertion and excitement may induce

them Fatigue indigestion cerebral lesions and hypertension render them more likely or may even cause them on occasion Certain poisons infections and internal diseases are sometimes associated with the appearance of pre mature beats Individual susceptibility is an important factor as shown by the induction of extrasystoles in some persons and not in others by tobacco tea coffee alcohol and certain drugs Finally heart disease itself favors the occurrence of premature beats and seems occasionally to be a direct cause but many persons with heart disease do not have premature beats and vice versa

Sex Both sexes frequently show premature beats the male sex more often as evidenced by a series of 218 cases of my own with a slight preponderance of males (123 95) (White 1926)

Age Premature beats may occur at any age they are however most com mon (in fact almost universal) in old age and rare in infancy and early child hood

Pathology There are no specific lesions of heart or nerves associated with premature beats Organic heart disease may or may not be present when it is the myocardium itself is usually normal except for hypertrophy Given a person with premature beats the chances are more than ten to one that no significant structural abnormalities of the heart are discoverable Premature beats are however relatively more numerous in the presence of heart disease than in its absence this is probably to be explained by the strain on the heart muscle resulting from some defect like valvular disease hypertension or coro nary disease

It is convenient and of some clinical value to separate premature beats into two main groups namely atrial and ventricular according to their point of origin Ventricular premature beats are much more common than atrial pre mature beats the ratio being about two to one the ventricular premature beats are less important clinically Atrial premature beats although often occurring without any discoverable cardiac lesions are more likely than are ventricular premature beats to be found in heart disease especially when there is mitral stenosis they then may be the precursors of atrial fibrillation Premature beats arising in the atrioventricular junctional tissues may be classed with ven tricular premature beats so far as their clinical significance is concerned

Symptoms There may or may not be symptoms with premature beats Probably at least one half of all individuals with this arrhythmia are uncon scious of its presence and its discovery in these individuals is an accidental finding on some routine examination Often however the occurrence of the premature beat is felt as a more or less disagreeable sensation due less to the abnormal beat itself than to the pause which follows it to the vigorous thump of the first normal beat after the pause or to the pressure wave forced up into the neck veins from the right atrium at the time of the premature beat this pressure wave results from the contraction of the atria while the ventricles are in systole The sensation may include two or all three of these elements but it is rarely very disagreeable

The occurrence of many premature beats may at first cause much discomfort but if these beats are continually recurring they tend gradually to lose their irritating character and finally they are scarcely or not at all noticed

It is however true that persons with coronary insufficiency may have painful premature beats for the same reason that such individuals with paroxysmal tachycardia may have a status anginosus during the rapid heart action because of the inability of the myocardium to be properly oxygenated during such hort diastolic rests quinidine may be very beneficial in such cases this may help to explain its usefulness on occasion in angina pectoris Sometimes in hypersensitive subjects pain may actually be felt with each abnormal contraction and a severe neurosis may result An erroneous diagnosis of angina pectoris has frequently been made in these individuals careful study easily prevents such gross error

When premature beats are so numerous that they interfere with the circulation as in rare instances when they occur in short series or more often than the normal beats dizziness and faintness may result but such symptoms are more likely to be due to an associated nervous reaction If the premature contractions occur as interpolated beats that is, between two normal beats without pause or in short runs the subject may be conscious of a slight fluttering sensation during the period of the three beats occurring in rapid succession

Signs The pathognomonic sign of a premature beat is its prematurity which may be discovered by auscultation of the heart itself by palpation of the arterial pulse by inspection of the jugular pulse or by the study of graphic records Feeling the pulse at the wrist is usually the least satisfactory way of detecting the premature beat for two reasons In the first place the abnormal beat is always relatively later in appearance in the pulse cycle at the wrist than at the heart a weak beat traveling more slowly along the arteries than a normal strong beat therefore a premature beat which is but little premature may not be noted as such by the finger on the radial pulse Secondly if the beat is very premature and weak it may not reach the radial artery at all or have sufficient force to be felt the resulting long pause may then be wrongly attributed to partial heart block or to sinus bradycardia rather than to the actual premature beat arrhythmia

Blood pressure studies show almost invariably a lower systolic and smaller pulse pressure with a premature beat than with a normal beat and sometimes there may be no measurable pressure at all Infrequently the premature beat occurs so early that there is not enough intraventricular pressure to raise the semilunar cusps and only a first heart sound is heard sometimes very faintly coming like a third heart sound or a reduplicated second sound of the preceding normal beat (*frustrane contraction*) Occasionally a considerable pulse deficit (the difference between apex and radial pulse rates) may be found if many very early or weak premature beats occur the radial rate may be half the apical in bigeminal rhythm

For complete analysis of a premature beat electrocardiograms are essential mechanical graphic records of arterial venous or cardiac pulsation are in

fenor Usually it is immaterial to know whether a premature beat is of atrial or of ventricular origin or in what part of atrial or ventricular tissue it arises and the discovery of premature beats on auscultation of the heart or on palpation of the pulse may not need further detailed study It is well however when possible to identify atrial premature beats for they often do presage paroxysmal tachycardia or atrial fibrillation It is still more important to look for alternation of the pulse that may be revealed by a premature beat and which is of so much greater significance than the premature beat itself (see Chapters 8 and 30)

The differentiation between atrial and ventricular premature beats in the absence of a phlebogram or an electrocardiogram lies in the presence or absence of a compensatory pause This as a matter of fact is a very rough and unreliable criterion even with graphic records of the arterial pulse Slight differences of time that may differentiate between a compensatory pause and one that is not fully compensatory are difficult or impossible to measure by finger ear or even sometimes by arteriogram A more important source of error is the fact that a ventricular premature beat may not be followed by a compensatory pause if it induces a backward-coursing or retrograde atrial contraction as it sometimes does thus breaking up the dominant rhythm Moreover a ventricular premature beat may be succeeded by atrioventricular nodal escape or by sinus arrhythmia and quickening of rate which occur occasionally to interfere with the application of the principle of the domi nant rhythm At times too an atrial premature beat is followed by a pause that is unusually long either because of succeeding sinus arrhythmia and bradycardia or because the site of abnormal stimulus production in the atrium is so far from the *sinoatrial node (for example in the left atrial appendage)* that the time expended in traveling back to the node to interrupt its rhythm and the time between the previous normal beat and the premature beat make an interval that is almost indistinguishable from the usual normal time interval

The electrocardiogram has the great advantage of revealing the presence and type of a premature beat by mere inspection usually without the need of any measurement whatsoever the premature beat is almost always ectopic in origin and so it is of abnormal shape in the electrocardiogram It is possible by this method of study to determine roughly the site of the abnormal impulse in the atria or in the ventricles For example a deeply inverted *P* wave usually indicates that the ectopic focus is far from the sinoatrial node and located near the atrioventricular node or in the left atrium although exact localization is as yet impossible (Figure 154) There are also fairly characteristic shapes for the complexes of so-called basal or right and of so-called apical or left ventricular premature beats as already noted above (Figure 155)

Course and prognosis A few premature contractions of the heart may occur for a short interval of time (an hour or a day) and never return so far as we know or they may come at more or less frequent intervals once - once an hour once a minute or at frequent often regular intervals e second beat or very rarely they may be more numerous than the

When they occur every second beat they give rise to a coupled rhythm or bigeminal pulse or if they are too weak to reach the radial pulse a slow regular rhythm at one half the apex rate is felt at the wrist When they occur every third beat they cause a trigeminal pulse at the apex and ordinarily at the wrist or a bigeminal pulse if they fail to reach the wrist. If they are interpolated there are regular sequences of three beats in rapid succession at the apex and wrist or if the interpolated beats fail to reach the radial pulse there is a pseudo-alternation every other normal beat following the premature beat being late and small When the premature beats occur every fourth beat they give rise to a quadrigeminal pulse at apex and wrist or to a trigeminal pulse at the wrist if they fail of transmission

The premature beat is of no clinical importance except in five respects In the first place individuals with heart disease show relatively a higher incidence and greater frequency of occurrence of premature beats than do those with normal hearts even though the absolute incidence of premature beats is greater in persons without heart disease Secondly ventricular premature beats occurring every other beat or in pairs after every normal beat and those which show by electrocardiogram two or more different shapes and directions of complexes especially if they alternate in shape and direction are evidence of a serious toxic or otherwise irritable state of the myocardium and demand careful study and treatment Thirdly the premature beat is sometimes a source of great discomfort or fear that must in itself be treated Fourthly painful premature beats induced by effort may prove to be confirmatory evidence of the presence of coronary insufficiency And finally the premature beat is now and then directly traceable to some toxic substance like digitalis or tobacco the reduction or omission of which suffices to get rid of the arrhythmia In the case of digitalis poisoning there may be a bigeminal or coupled rhythm with or without atrial fibrillation due to the regular occurrence of ventricular premature beats the appearance of this arrhythmia in the course of administration of large doses of digitalis indicates that a considerable percentage of a lethal dose has been given probably close to 75 per cent

The diagnosis and prognosis of heart disease depend not on the presence or absence of premature beats but almost entirely on other evidence of trouble as Mackenzie so clearly pointed out

Mackenzie J "The Extra systole" Chapter XXVII of *Diseases of the Heart* 3rd ed London 1913 page 199

Extra systoles or intermittent heart as they are sometimes called occur so frequently and are viewed by the profession so seriously that it is necessary to indicate their bearing on the individual's future Hitherto their cause has been unknown and individuals showing them have been considered unfit for admission into the services military naval and civil and have been considered unsuitable for life premiums and they have been made miserable for life by the vague prognostications of danger and have been subjected to prolonged and quite unnecessary treatment

"The fact that the occurrence of an extra systole is due to some part of the heart s structure being temporarily more excitable than the normal starting place has led to the idea that it may be an evidence of some disease process A certain amount of confirmatory evidence for this supposition is found in the fact that people with undoubted disease of the heart do show extra systoles and that extra systoles have sometimes been found to precede the appearance of grave disturbances of the heart s action as auricular fibrillation (Case 51) For these reasons there has been a tendency to view extra systoles as signs of some gravity If however the subject be studied from a wider and more practical outlook it will be found that extra systoles in themselves are not signs of any specific injury to the heart nor should a prognosis of any gravity be based on their appearance alone I have watched individuals for over twenty five years who have presented extra systoles sometimes with greater frequency than at other times and these people have led laborious lives and have never shown the slightest symptoms of heart failure or any other evidence of heart impairment. I have had similar experiences with people who have shown all forms of extra systole auricular ventricular and nodal I have watched young people grow into manhood and lead vigorous lives I have watched elderly people live beyond 80 years of age in whom I had detected extra systoles at the age of 60 and when they did die the cause of death was not primarily cardiac failure A short time ago I was consulted by a man aged 69 years whom I found in a fair state of health He presented auricular extra systoles at frequent intervals and when I remarked upon this he told me that they had been present for over fifty years Time and again he had submitted to prolonged treatment without avail for the purpose of curing this irregularity He had oftentimes been made miserable and depressed by the grave prognostications of his medical advisers and had up to the time when I saw him been under the apprehension that he had some obscure heart affection which might prove fatal at any moment

From such facts as these that healthy men and women may present this form of irregularity it can be gathered that extra systoles in themselves are signs of no significance so far as the efficiency of the heart is concerned.

It may therefore be stated that when the extra systole is the only abnormal sign the prognosis is a favourable one and where it is associated with other signs the prognosis is to be based upon these other signs

Treatment As a rule premature beats in themselves demand no treatment Complete reassurance as to their significance can and should almost invariably be given If there is heart disease or other illness treatment should be directed toward such disease without regard to premature beats unless these abnormal beats cause much discomfort in themselves or unless they are evidence of poisoning by something which can be easily controlled If there is no evidence of any disease and the premature beats do not occasion much distress reassurance usually suffices to relieve the individual of his fear and much of his consciousness of their presence It is usually best to tell the patient of the finding of premature beats even when he does not feel them in order to prevent his being unduly alarmed if they are later discovered and taken too seriously by some physician or if their existence becomes evident to the patient himself

Often the successful treatment of or the spontaneous recovery from whatever disease is present suffices to get rid of the premature beats For example digitalis which in full dosage may cause premature beats may also actually dispel them either directly or as the result of successful treatment of an associated heart failure digitalis however much more often causes than dispels premature beats

If some factor like tobacco alcohol fatigue or constipation appears responsible for premature beats or is attended by their presence control of this factor generally an easy matter may suffice to abolish the premature beats Operative correction of some trouble such as gallstones has also been known to be followed by a disappearance of premature beats Usually however no special measures are effective and the premature beats come and go without possibility of their control

When premature beats are especially annoying and occasion because of the discomfort they cause a real state of ill health in themselves sometimes amounting even to a partial or complete invalidism careful redirection of the patient s mental and emotional outlook should be undertaken and various drugs may also be tried The six drugs most likely to help are in their order of choice (1) quinidine sulfate as a 0 2 gm (3 gr) tablet three or four times a day (2) for ventricular (not atrial) premature beats procaine amide (Pronestyl hydrochloride) in the dosage of 0 5 to 1 0 gm (one tablet = 0 25 gm) orally every three to six hours (3) potassium salts for example, 2 to 4 gm (30 to 60 gr) of the acetate in 25 per cent solution in peppermint water every 4 to 6 hours especially effective in the case of premature beats due to digitalis intoxication (Sampson and Anderson 1932) (4) bromides preferably ½ to 1 gm (7½ to 15 gr) of triple bromides (of sodium potassium and ammonium) in solution in a few ounces (60 to 90 cc) of water two or three times a day (5) digitalis as a pill of the powdered leaf standard strength (see Chapter 30) 0 06 gm (1 gr) three times a day for a week and (6) papaverine hydrochloride 1½ gr four times a day In various cases each one of these remedies has proved effective but in many cases no one of them controls the premature beats Bromides should be used for short periods of time only because of the hazard of toxic effects Strychnine given with quinidine has also been recommended when quinidine alone is not effective (Carter and Trant 1935) The very absence of specific therapy however has flooded the market with remedies of reputed but doubtful value

Differential diagnosis Premature beats must be differentiated from sinus arrhythmia and heart block This can in most cases be done easily without an electrocardiogram and in doubtful cases easily with such a record The usual disappearance of premature beats caused by increasing the heart rate by exercise helps to differentiate a gross arrhythmia due to many premature beats from the absolute arrhythmia of atrial fibrillation which increases on exercise The clear prematurity of a cardiac contraction followed by a pause longer than the usual interval between two normal heartbeats in an otherwise regular rhythm establishes the diagnosis of a premature beat Exceptions like interpolated premature beats needing graphic records have been discussed above

Premature beats are a sign of one type of irritable heart but their occurrence is not to be confused with the so-called irritable heart of soldiers' which in the vast majority of cases has proved to be neurocirculatory asthenia nor is it to be classed as cardiac neurosis although such a condition may be superimposed

And finally angina pectoris is not to be diagnosed when all that a patient complains of is a sharp stabbing pain in the precordium caused by a premature beat

PAROXYSMAL TACHYCARDIA

Paroxysmal tachycardia is a common disorder of cardiac rhythm closely related to premature beats first mentioned by the ancients in particular Galen but not clearly recognized as a characteristic disorder until Bristowe described it in 1888 it was given its name the following year by Bouveret (1889)

Bristowe J S On Recurrent Palpitations of Extreme Rapidity in Persons Otherwise Apparently Healthy *Brain* 1888 X 164

This paper by Bristowe clearly describing paroxysmal tachycardia as a clinical entity for the first time antedated by a year the report by Bouveret in which the term paroxysmal tachycardia was first used The following quotations are of interest

'The subject to which I wish to direct attention is that of extremely rapid pulsation occurring for the most part in intermittent paroxysms of variable duration in hearts structurally and texturally sound and in persons otherwise healthy

That hearts may beat with the extreme rapidity with which I have found them to beat is a fact which I think has been largely overlooked and with which I at any rate had no practical acquaintance until within the last two or three years and yet I feel sure judging from my recent experience that the condition which I am about to discuss is of frequent occurrence and needs only to be looked for intelligently to be recognized in many persons who are regarded as merely nervous and liable to attacks of ordinary palpitation

So far as I know the literature of the subject was until recently limited to the report in the British Medical Journal for the year 1866 of three well marked cases the first from the pen of the late Dr Cotton and the others respectively by Dr James Edmunds and the late Sir Thomas Watson Of these cases I need only say that they almost accurately resembled the most striking and typical of the cases which are incorporated in this paper

'The first typical case of the disease which I ever fully recognized was one which I saw in consultation with Dr Wyman of Putney in the early part of 1885 The patient was a fairly healthy looking young married lady who had evidently been liable for some years to attacks of palpitation and was free from structural disease of the heart The attack in which I saw her came on suddenly without apparent cause and after a week left her as suddenly as it had arisen Her pulse varied between 180 and 192 in the minute A few weeks later she had a recurrence of palpitation when the cardiac beats were counted at 246 What seemed to me at the time the most remarkable feature of her case was the apparent absence of distress Had I not known that the patient s heart was beating with extraordinary rapidity it would

never have struck me from watching her and conversing with her that there was anything the matter with her

Bristowe then proceeds to relate eight other cases with or without heart disease and with or without arrhythmia attending the paroxysms of tachycardia One case was evidently an instance of atrial fibrillation and yet this patient a man 65 years old was able to run 3 miles in 20 minutes His first case described above may of course have had atrial flutter without block when the rate was 246 rather than the usual paroxysmal tachycardia (see Chapter 33) Among the conclusions of the paper the seventh is the most pertinent

7 As to the real nature of the disease which my paper is intended to illustrate I have little to say My belief is as will doubtless have been gathered from all that precedes that so far as the heart is concerned it is a purely functional disorder that any actual cardiac disease which may be present in any case must be regarded as accidental and that the slight hypertrophy and dilatation of the heart which may be found in patients who have suffered from the malady for years are (as I have already remarked) the consequence and not the cause of the palpitation.

Incidence Paroxysmal tachycardia is very frequent but not so universal as are premature beats Many individuals have short attacks of what they call fluttering of the heart for which they do not consult a physician either because the attacks are not sufficiently bothersome or because they are so brief that it would be useless to summon one if they do seek medical advice the paroxysms usually occur at times when they are not observed by the doctor Many healthy friends of mine have complained of such attacks lasting usually but a few seconds or minutes and not sufficient in severity or duration to render them of more than passing interest by special endeavor I have obtained electrocardiograms of some of these attacks when they have been repeated or have been longer than usual but such success is rare because of the elusive nature of the paroxysms These observations illustrate the frequency of the condition which is inaccurately represented in any statistical studies at present available such as my own of a series of 132 cases 89 (or two thirds) of whom showed no evidence of heart disease (White, 1926)

Ventricular paroxysmal tachycardia though often serious is a relatively uncommon type and is found only once to every six cases of atrial paroxysmal tachycardia in an electrocardiographic series of 103 cases of paroxysmal tachycardia at the Massachusetts General Hospital the origin of the abnormal rhythm was clearly in the atria in 80 and clearly in the ventricles in 14

Mechanism (abnormal physiology) Paroxysmal tachycardia appears to be due to a rapid usually regular production of waves of excitation and contraction at some point in the atrial or ventricular muscle generally outside the normal sinoatrial nodal pacemaker although rare instances of nomotopic or sinoatrial paroxysmal tachycardia have been reported Electrocardiographic study shows that the separate excitation waves closely resemble those of atrial or ventricular premature beats The exact mechanism of production of such a rapid succession of premature contractions is not clear theories have ascribed it to the rapid building up of a stimulus as in the case of normal sino-

atrial tachycardia which seems most likely or to constant circus movement of an excitation wave once started or to some other unknown cause Its main characteristics are its sudden onset and offset its rapid rate (120 to 200 or rarely somewhat more usually 160 to 180) and its tendency to great regularity In the rare paroxysmal tachycardia of infancy the heart may attain an *extraordinarily rapid rate of beating even at 300 or more The fastest rate that* I knew of at the time of the second edition of this book was in an infant whose heart rate was 312 the result of either atrial paroxysmal tachycardia with bundle branch block or ventricular paroxysmal tachycardia the infant died of bronchopneumonia erysipelas empyema and meningitis but showed no abnormality of the heart at autopsy (Lyon 1937) In 1937 Campbell reported three interesting cases of extremely rapid heart rates in infancy (300 274 and 266 respectively) two of whom had congestive heart failure during their paroxysms but recovered completely Later Hubbard published his important study of nine infants with paroxysmal tachycardia their rates were 270 300 274 300 260 290 305 270 and 220 respectively (Hubbard 1941) At the time of the third edition of this book (1944) I stated that I had seen electrocardiograms of a few very young infants with heart rates of 300 to 310 and had noted the remarkable case of a 10 day old infant with a heart rate of 345 reported by Puglisi (1939) Since then even faster rates have been noted for example 365 per minute unrecognized until just before death in the case of an infant (Silverman and Race 1949)

(a) *Atrial paroxysmal tachycardia* Atrial paroxysmal tachycardia (Figure 156) is by far the most common and least important type of paroxysmal tachy-

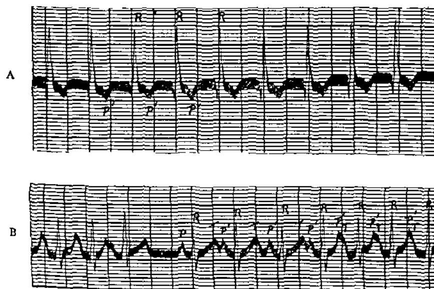


FIG 156 Electrocardiograms (Lead 2) *showing atrial paroxysmal tachycardia (A)* The usual mechanism (*B*) an unusual variation with short runs of tachycardia and varying rate

cardia occurring about six times more often than the ventricular type It is usually very regular at a rate of 160 to 180, but on rare occasions there may be a gradual onset gradual offset and some slight arrhythmia during its course The abnormal contractions are usually represented in the electrocardiogram by inverted *P* waves in Leads 1 and 2, diphasic *P* waves in Lead 3 and inverted *P* waves in the precordial leads but sometimes the *Ps* are upright with abnormal contour the appearance of these ectopic atrial complexes may vary considerably with change in position of the heart due to forced breathing the inverted *P* waves in Lead 2 during quiet breathing for example becoming diphasic or even upright on deep inspiration resulting from the changed relationship of the position of the ectopic focus and that of the heart The abnormal *P* waves in atrial paroxysmal tachycardia are usually followed by normal ventricular responses at the same rate but occasionally when the rate is very rapid there may be temporary atrioventricular or intraventricular block so that 2 to 1 partial block or left or right bundle branch block may appear as a transient associated functional disorder of little or no clinical importance in itself Rarely an atrial paroxysmal tachycardia may be interrupted by a ventricular premature beat

(b) *Ventricular paroxysmal tachycardia* Paroxysmal tachycardia of ventricular origin (Figure 157) is an important frequent and usually a serious disturbance of rhythm similar in other characteristics to atrial paroxysmal tachycardia except that it tends to be somewhat less regular in its rhythm The arrhythmia although obvious on electrocardiographic measurement is evident clinically in only about half of the cases on close examination The shape of the ventricular complex of the electrocardiogram is exactly like that of a ventricular premature beat but in a few instances there is a variation in shape from beat to beat in the most marked cases an alternate reversal of direction with slight alternation of time intervals (Figure 157C) When an alternating bidirectional character of the ventricular complexes of ventricular paroxysmal tachycardia is seen the condition is invariably a serious one usually terminal The fundamental sinoatrial rhythm may or may not be disturbed by a paroxysm of ventricular tachycardia usually it is at least quickened even though it may remain independent sometimes retrograde atrial responses follow each or every other abnormal ventricular beat in this variety of tachycardia On occasion atrial fibrillation and very rarely atrial paroxysmal tachycardia may coexist with ventricular paroxysmal tachycardia The differentiation of abnormal ventricular tachycardia into right ventricular and left ventricular types has been suggested as in the case of ventricular premature beats (see Chapter 9 and the first part of the present chapter) but as yet the clinical value of such differentiation has not been shown

(c) *Atrioventricular nodal paroxysmal tachycardia* This is very rare It has the relatively unimportant clinical significance of atrial paroxysmal tachycardia and a mechanism somewhat similar to that of ventricular paroxysmal tachycardia with regular retrograde atrial response although in rare instances

the atrial contraction may precede the ventricular even when the impulse starts in the atrioventricular node

Electrocardiographic records are needed to differentiate clearly the different types of paroxysmal tachycardia a phlebogram if it happens to show the onset or offset of a paroxysm gives a certain amount of information but not clear enough proof

A very interesting small group of cases of paroxysmal tachycardia atrial mostly but sometimes ventricular consists of otherwise healthy young people who show by electrocardiogram either constantly or temporarily short *P R* intervals *This syndrome will be discussed further in Chapter 34 but a clearer*

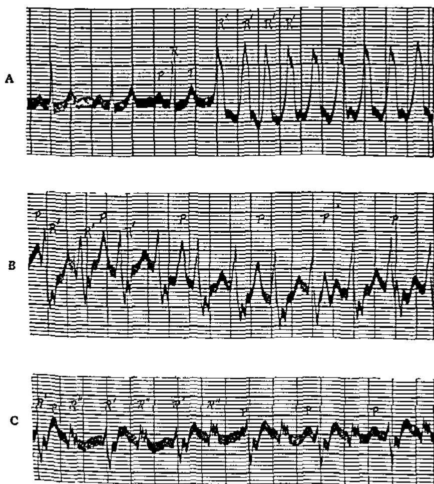


FIG 157 Electrocardiograms (Lead 2) showing ventricular paroxysmal tachycardia (*A*) onset of the usual type (*B*) with *P* waves clearly seen superimposed on the *QRS* and *T* waves and quite independent of them and (*C*) with ventricular complexes alternating in direction (also called "bidirectional)

understanding of the mechanism of this syndrome might throw light on the mechanism of paroxysmal tachycardia itself

Etiology *Cause* Just how the abnormal mechanism of paroxysmal tachycardia is initiated is not known but certain causative factors are known Conditions responsible for premature beats are likewise responsible for atrial paroxysmal tachycardia Such factors are fatigue sudden exertion indigestion tobacco alcohol digitalis poisoning infection and heart disease As in the case of premature beats heart disease is more often absent than present when there is atrial paroxysmal tachycardia, though here again a diseased heart is more often affected by paroxysmal tachycardia than is a normal heart. Often there is no known or discoverable cause for atrial paroxysmal tachycardia

Ventricular paroxysmal tachycardia is found as a rule but not always in the presence of organic heart disease of serious type and can be rapidly fatal if the electrocardiogram shows alternating direction of the complexes Digitalis intoxication has been associated in a number of the fatal cases on record In a few instances ventricular paroxysmal tachycardia occurs with little or no evidence of organic heart disease

Sex Both sexes are probably affected about equally by paroxysmal tachycardia of either atrial or ventricular type In the series of my own of 132 cases noted above the females were preponderant in the ratio of 82 to 50 but in another electrocardiographic series of 80 cases of atrial paroxysmal tachycardia 42 were male and 38 were female while of 13 cases of ventricular paroxysmal tachycardia proved electrocardiographically 8 were male and 5 were female

Age Atrial paroxysmal tachycardia is common after childhood but rare in infants and young children Ventricular paroxysmal tachycardia rare at any age is commonest in the serious heart disease of later life

Family incidence It is not uncommon for paroxysmal tachycardia to occur in several members of the same family

Pathology There is no pathologic condition in the heart characteristically found with paroxysmal tachycardia most cases of this disturbance of rhythm have apparently perfectly normal hearts There are however certain changes which favor paroxysmal tachycardia Mitral stenosis is not infrequently accompanied by atrial paroxysmal tachycardia before the onset of permanent atrial fibrillation but paroxysmal atrial fibrillation which also occurs in mitral stenosis must be differentiated from atrial paroxysmal tachycardia The heart in thyrotoxicosis may be affected by either atrial paroxysmal tachycardia or paroxysmal atrial fibrillation but more commonly by the latter And finally cardiac infarction is likely to be found responsible in the more serious cases of ventricular paroxysmal tachycardia

Symptoms Usually the person affected is conscious of the disturbance of rhythm but in rare cases a paroyxsm long or short may pass unnoticed except by the observer this happens in insensitive persons or in individuals who are too ill to appreciate this complication The general complaint is of a regular rapid palpitation or of a disagreeable sensation of fluttering in the

chest in the region of the heart The sensation may be widely referred over the body so that the vessels seem to pound in head and arms abdomen and legs A fullness in the neck is often complained of due to the transmission of the pulsation to the jugular veins There may or may not be associated dyspnea and heartache due in part and in all probability chiefly to nervousness and fear in sensitive persons and representing a kind of neurocirculatory asthenia but dyspnea may also be due to cardiac fatigue in persons with hearts already weakened or overburdened or occur after very long paroxysms lasting for days Angina pectoris has sometimes been noted during the paroxysms in persons with coronary heart disease to start with giving rise to a *status anginosus* until the paroxysm subsides and symptoms of congestive failure with engorgement of liver and lungs are occasionally produced by long paroxysms of tachycardia in patients with heart disease and rarely in persons without heart disease With an extremely rapid rate in paroxysmal tachycardia the brain may receive little blood and faintness dizziness and even syncope may ensue If the pulse is faint or absent and unconsciousness and convulsions result from the extreme tachycardia the condition may simulate the Morgagni Adams Stokes syndrome of high grade heart block An occasional symptom during or following paroxysmal tachycardia is increased frequency or increased amount of urination doubtless a nervous reflex in large part

Signs The pathognomonic evidence of paroxysmal tachycardia is electro cardiographic (Figures 156 and 157) but any regular rapid rate of 120 to 200 per minute observed clinically to start abruptly and to stop abruptly and lasting usually a few minutes (with a range from a few seconds to several days) may be reasonably diagnosed as paroxysmal tachycardia without the need of graphic records A striking feature of paroxysmal tachycardia is the uniformity of rate as compared with ordinary sinoatrial tachycardia which varies in rate under various conditions such as exercise change of position carotid pressure deep breathing and digitalis therapy A variation of a few beats per minute may however occur from time to time even in paroxys mal tachycardia especially of the ventricular type and especially under the influence of quinidine

Aside from the tachycardia there is usually no other sign There may or may not be evidence of chronic heart disease and enlargement Except when the heart is exhausted or diseased it is usually found by roentgen ray examina tion during a paroxysm to be decreased slightly or moderately in size below the normal this is due to the fact that the rapid rate prevents full normal diastolic dilatation Sometimes even in the case of normal hearts prolonged paroxysmal tachycardia may cause cardiac dilatation which is evident by roentgen ray The blood pressure is usually normal or somewhat decreased during a paroxysm and the pulse small due to the rapid rate At times during a very rapid heart rate or after a long paroxysm alternation of the pulse occurs due doubtless to myocardial fatigue (Figure 33 page 162) pulsus alternans is not then the serious sign that it is with slower pulse rates the faster the heart rate the less important the pulsus alternans It is probable

that a healthy heart beating at a rate of nearly 300 per minute should normally show alternation of the pulse The occasional development of intraventricular block at very rapid heart rates is likewise a more or less ' normal physiologic condition

Signs of congestive failure may be found to begin or to increase in cases of heart disease during paroxysms of tachycardia Very rarely a long paroxysm at a very fast rate may give rise to signs of failure even in the absence of heart disease this is especially true of the extreme tachycardias in infants whose hearts and livers may become very large shrinking rapidly when the attacks cease (Hubbard 1941)

Electrocardiographic study is helpful during a paroxysm of tachycardia particularly in differentiating the atrial type from the ventricular and in excluding atrial flutter Following a prolonged or very severe paroxysm of tachycardia the *T* waves of the electrocardiogram may become inverted even for some days and even in the absence of heart disease due evidently to myocardial fatigue (Campbell 1942)

Course and prognosis Atrial paroxysmal tachycardia is usually unimportant. It is a transient disturbance as a rule lasting but a few seconds or a few minutes and only rarely more than a few hours sometimes occurring but once and sometimes repeatedly over a short space of time (a few days or weeks) It tends to recur off and on through life but often at long intervals (years for example) It generally neither shortens life nor limits activity but in some cases it necessitates rest during the paroxysms and if the paroxysms are long or numerous there may be much crippling in a few cases complete invalidism may result Heart failure and death are very rarely induced by paroxysmal tachycardia in a patient with heart disease except in the case of atrial paroxysmal tachycardia complicating marked mitral stenosis or other pathologic condition where the cardiac reserve is low and failure easily induced and in the case of ventricular paroxysmal tachycardia which may be itself a terminal condition rather than a cause of death

Like premature beats paroxysmal tachycardia of atrial origin cannot be considered to be a diagnostic or prognostic sign of any importance Diagnosis and prognosis must be based on other findings Paroxysmal tachycardia of ventricular origin on the other hand must be considered serious until proved unimportant

Complications Only rarely is paroxysmal tachycardia attended by complications The most important ones are (1) congestive heart failure in the presence of pre-existing heart disease and even without previous heart disease especially if as in infants the heart rate is excessively fast (300 more or less per minute) (2) myocardial infarction in the presence of a high degree of coronary artery narrowing and due to the abrupt drop in effective coronary blood flow (3) the temporary status anginosus in coronary heart disease without actual infarction (4) syncope which may be either a nervous reaction the result of marked decrease in cerebral blood flow during the paroxysm or due to a transient total cardiac standstill at the end of the paroxysm and before

the resumption of normal rhythm and (5) death from evolution of ventricular tachycardia into ventricular fibrillation

Treatment Usually no treatment of atrial paroxysmal tachycardia is needed if the attacks are brief and rare that is not more than ten or fifteen minutes long or oftener than once a month If the paroxysms are long or frequent, however or even if they are short and infrequent but disagreeable an attempt should be made to abolish them

The treatment consists of therapy directed to stop the individual attack and of therapy to prevent a recurrence of paroxysms

(a) *Therapy of an attack of atrial paroxysmal tachycardia* should be as simple as possible and not include the administration of a great variety of unreliable remedies to which recourse is frequently had

The following procedure has been found in the hands of experienced observers to be a good one to adopt In the first place it is usually wiser for the patient to remain quiet during the paroxysm seated or recumbent than to continue full or even partial activity although it is possible and sometimes necessary to complete a task or effort in progress at the time of the onset of the paroxysm Usually the paroxysms are shorter during rest than during exercise but occasionally the reverse is true and if so exercise should be prescribed especially calisthenic motions of arm stretching or body bending which may cause an abrupt cessation of the attack Even in the resting position certain postures are sometimes uniformly or frequently effective in stopping paroxysms for example leaning forward in a chair with the head low or lying with the head lower than the rest of the body

If the paroxysm does not stop quickly after the patient has assumed the most satisfactory position it is always worthwhile to try the effect of stimulation by firm carotid sinus pressure with the tips of two or three fingers for from five to thirty seconds high on the right side of the neck over the fullest carotid pulsation If pressure on the right side is ineffective the same procedure may be tried on the left side or moderately firm pressure with the finger tips may be exerted on either eyeball with the eye closed (oculocardiac reflex method) In about 10 per cent of all cases the reflex vagal effect of these pressure methods or of position changes are effective and the paroxysms stop abruptly and dramatically usually with great relief to the patient Since these procedures are easy and with rare exceptions safe they are always to be recommended Right carotid sinus pressure should be tried before the left and before ocular pressure since it is more likely to be effective and since pressure on the neck is less disagreeable than that on the eyeballs In very rare instances carotid sinus pressure has been followed by cerebral vascular accidents such as thrombosis but I myself have never encountered such sequelae Various other mechanical and reflex measures have been utilized in individual cases with occasional success such as the induction of vomiting firm abdominal pressure application of an ice bag over the precordium drawing out the tongue forced respiration and the Valsalva or Muller experiments (the former consisting of an attempt to expire forcibly with the glottis closed after

a deep inspiration and the latter being an attempt to inspire forcibly with the glottis closed after a deep expiration) but these measures are not to be routinely recommended Often the paroxysm ceases spontaneously and the particular measure being tried at the time may unjustly be credited with the cure

Drug therapy of a paroxysm is often unreliable The best all around drug to try first is quinidine which may be employed if a paroxysm is long (more than an hour), distressing or exhausting Quinidine sulfate in tablet or powder form may be given by mouth (0 4 gm or 6 gr every two hours for five doses under observation) this oral therapy has proved to be effective in cutting short the paroxysms in frequent cases in my experience and in that of others but it cannot always be relied upon In patients severely ill with ventricular (and in fact also atrial) paroxysmal tachycardia who have failed to respond to quinidine by mouth or who are too nauseated to take it a convenient and effective method of treatment is the subcutaneous injection of 1 gm (7½ gr) of quinidine lactate or hydrochloride (injectable) every 2 hours until the paroxysm ends or toxic symptoms of cinchonism appear Intravenous injection of 0 2 to 0 4 gm of quinidine lactate or sulfate directly and repeated every four hours as needed or in the form of a drip (3 3 gm or 50 gr dissolved in 500 cc normal saline or in 5 per cent glucose solution) administered until there is an effect has also been recommended occasionally striking benefit has been reported from this measure but it is simpler safer and about as effective to give the drug by mouth or to use quinidine salts intramuscularly

Another drug that has been used to control paroxysmal tachycardia especially by Starr and his associates (1933) is Mecholyl (acetyl B methylcholin chloride) which acts through its stimulation of the parasympathetic nerves (including the vagus) the Mecholyl was successful in from one half to twelve minutes in abolishing twenty four attacks of paroxysmal tachycardia ventricular or atrial in nine patients of Starr s when injected subcutaneously in the dosage of 20 to 30 mg it may however have untoward effects consisting of the production of vomiting dyspnea asthma (stopped by atropine) pain marked fall of blood pressure and heart block Atropine sulfate (1 mg or 1/60 gr in solution) should be at hand to inject immediately in case of toxic symptoms Recently Mecholyl in larger dosage 200 to 300 mg has been found to be effective when given intranasally (Nathanson and Tober 1948)

More recently revived as drug therapy to induce vigorous central vagal stimulation by means of marked nausea is the administration of syrup of ipecac by mouth 8 to 16 cc (2 to 4 drachms) at a dose repeating it as needed to build up a vagal stimulation marked enough to stop the paroxysm of tachycardia or at least to induce vomiting this measure is usually effective and not dangerous but it is disagreeable and to be reserved for the most severe cases.

If a patient is in much distress and the paroxysm continues despite the measures described above various other drugs may be tried Bromides may be administered 1 gm (15 gr) of the triple bromides every four hours for a few doses as needed or rarely morphine 0 01 to 0 015 gm (1/6 to 1/4 gr) intra

venously or subcutaneously it is however very important to avoid using morphine except in the rarest cases of severe prolonged pain pulmonary edema or shock or obstinate ventricular tachycardia because of the very real possibility of establishing morphinism in the treatment of this disorder which is so often recurrent Also bromides should be used for only short periods of time because of the hazard of toxic effects In a few cases digitalis intravenously (two or three doses of 0 2 to 0 4 mg of digitoxin or of 0 1 to 0 5 gm of Digifolin Digalen or similar preparation for intravenous administration in 10 per cent solution at intervals of four hours) or strophanthin intravenously 0 5 to 0 25 mg or (1/120 to 1/240 gr) once has been followed by a rapid cessation of a paroxysm of tachycardia but often this treatment is ineffective it should be tried only if other measures in the control of an obstinate attack have failed or if there are symptoms and signs of congestive failure In infants with prolonged paroxysmal tachycardia at excessive rates Hubbard found that digitalis (Digifolin) in the dosage of 0 1 to 0 3 gm daily for one or two days was usually very effective and should be used at once in preference to any other treatment (Hubbard 1941)

Another therapeutic measure which has been tried and recommended in cases of intractable paroxysmal tachycardia is the injection of novocaine (procaine) and of alcohol in the stellate ganglion left or right (Coleman and Bennett 1938 Leibovici et al 1939)—this procedure needs further testing before adoption since it is still only in the experimental stage Somewhat related has been the successful control of disturbing paroxysmal tachycardia occurring during cyclopropane anesthesia by the intravenous injection of pro caine (0 1 per cent solution) (Kraft 1947) Finally magnesium sulfate in 10 per cent solution by slow intravenous injection (2 gm in 5 minutes) has been recommended

(b) *Therapy of an attack of ventricular paroxysmal tachycardia* A parox ysm of ectopic ventricular tachycardia is as a rule much more serious than a paroxysm of ectopic atrial tachycardia and therefore demands almost in variably emergency treatment This consists of the use of quinidine or of procaine amide (Pronestyl) Quinidine may be given in the form of the sulfate by mouth dosage of 0 4 gm (6 gr) to be repeated in one hour and again in another hour if the attack is still in progress unless the situation is very urgent under which conditions the drug should be given intramuscularly in the fo m of the lactate gluconate or hydrochloride (injectable) Ampoules of solutions of these salts have been prepared for ntramuscular use 0 4 to 0 6 gm (6 to 9 gr) should be given and repeated at two hour intervals for several doses if necessary Although intravenous medication has been used it is less desirable because of its toxic effects Sedatives and even narcotics may be needed also especially if the ventricular tachycardia induces severe dyspnea with pulmonary edema or status anginosus

Recently procaine amide (Pronestyl hydrochloride) has been introduced both in the treatment and prevention of paroxysms of ventricular tachycardia It is the most effective therapy yet found and is given in the dosage of 0 5 to

1 0 gm orally or intravenously the latter in 5 to 10 cc solution It can be repeated at two hour intervals as needed in direct therapy and every three to six hours orally as a prophylactic

(c) *The prevention of paroxysms of tachycardia* is just as uncertain as is the treatment of an individual attack In the first place possible factors responsible for the occurrence of the paroxysms should be sought and eliminated such factors may be fatigue overuse of tobacco tea or coffee constipation indigestion overeating overexertion focal infection and heart failure In the second place there are certain positive measures which are sometimes effective Quinidine sulfate in daily rations constantly or at intervals (0 2 gm or 3 gr in tablet or powder form three or four times a day) is frequently beneficial reducing or abolishing the paroxysms in about half the cases In rare individuals when the quinidine is ineffective digitalization may work well at least it is worth trying in obstinate cases in the dose of 0 06 gm (1 gr) of the powdered leaf (of the new international and U S P standard strength—see Chapter 29) in pill form three times a day for a week for an adult of average size then if effective the digitalis may be continued in daily rations of 0 06 gm (1 gr) for as long as necessary It is to be remembered that toxic doses of digitalis may themselves cause paroxysmal tachycardia especially of ventricular type Potassium salts have also been recommended for obstinate tachycardia as in the case of premature beats Stempien and Katz (1942) for example have advised giving 1 or 2 gm of potassium chloride or acetate every two to four hours to supplement or reinforce the action of quinidine Bromide therapy 1 gm (15 gr) of the triple bromides once or twice a day may be useful in relieving the discomfort and worry caused by the paroxysms even if not in reducing the number and duration of the paroxysms themselves Finally thoracic sympathectomy has been introduced to prevent or to decrease the incidence of obstinately recurrent paroxysmal tachycardia but with as yet inconclusive results

Reassurance is always an important part of the treatment and may itself suffice to get rid of the major part of the patient s unfavorable reaction to the attacks Moreover daily exercise in the open air may have a salutary influence on an irritable heart

Differential diagnosis Paroxysmal tachycardia must be differentiated from extreme sinoatrial tachycardia atrial flutter and atrial fibrillation Its steady rapid rate and sudden onset and offset distinguish it from sinoatrial tachycardia Its short duration (seconds minutes or hours rather than days weeks months or years) the slower atrial rate (100 to 200 rather than 200 to 400) and the failure of atrioventricular block to be an almost constantly associated condition distinguish it from atrial flutter Its regularity of rhythm distinguishes it from atrial fibrillation To differentiate atrial from ventricular paroxysmal tachycardia with certainty an electrocardiogram is necessary, though clinically a slight arrhythmia favors the diagnosis of the ventricular type

Finally the abruptness of the paroxysms of tachycardia may now and then result in confusion with heart attacks other than arrhythmias especially

angina pectoris coronary thrombosis and acute dyspnea careful analysis should easily prevent such confusion except perhaps in rare cases actually suffering from two different kinds of heart attacks occurring simultaneously (in which case the tachycardia may induce anginal pain or acute heart failure) or occurring alternately

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CHAPTER 33

ATRIAL FIBRILLATION AND FLUTTER VENTRICULAR FIBRILLATION QUINIDINE THERAPY

Although it is quite possible that atrial fibrillation and flutter are as mani festations of abnormal physiology simply more advanced stages of the same process that gives rise to atrial paroxysmal tachycardia they are so different clinically from that disorder of rhythm that they demand an entirely separate chapter

Moreover although atrial fibrillation and atrial flutter are themselves very clo ely related in mechanism undoubtedly representing simply different stages or gradations of the same underlying process or disturbance of cardiac rhythm they do not however have the same clinical characteristics and they differ somewhat in treatment They will therefore be considered separately in this chapter Atrial fibrillation though apparently a more complicated mechanism than atrial flutter is far more common and clinically more important and so will be considered first

ATRIAL FIBRILLATION

Introduction Atrial fibrillation is one of the commonest most interesting and most important disorders of cardiac rhythm it is fundamentally a dis turbance of atrial origin and attended usually by absolute irregularity of ven tricular action Its clinical existence suspected by Hering in 1903 and by Cushny and Edmunds in 1906 was proved in 1909 by Rothberger and Winterberg and by Lewis independently

Rothberger C J and Winterberg H Vorhofflimmern und Arhythmia perpetua *Wien klin Wchnschr* June 17 1909 XXII 839

Rothberger and Winterberg were the first to publish satisfactory evidence that atrial fibrillation occurs in human patients their publication antedated by only a few months the independent demonstration by Lewis that atrial fibrillation is a common clinical condition I have selected and translated a few sentences from this work of Rothberger and Winterberg

Although the pulsus irregularis perpetuus has been known to clinicians for a long time it has only in recent years been described by Hering (1903) as a special form of cardiac arrhythmia characterized by particular features

The normal venous pulse curve shows with each heart beat three characteristic upstrokes the first of which precedes the apex impulse that is the pulse in the great arteries and represents atrial systole

In arrhythmia perpetua this wave which gives us evidence of activity of the right atrium is entirely missing and the phlebogram shows the characteristics of the so called positive or ventricular venous pulse

There has long been known in animal experimentation a very irregular heart rhythm namely atrial fibrillation (Flimmern der Vorhofe) which is identical in all details with the signs of arrhythmia perpetua

Atrial fibrillation is accompanied by absolutely irregular ventricular action transmitted to the pulse this arrhythmia is of exactly the same character as that which we find in arrhythmia perpetua

In atrial fibrillation more or less delicate fibrillary movements occur which are of no significance for the movement of blood as a result in the phlebogram the preventricular wave is missing and a positive venous pulse develops

The authors then describe electrocardiograms from experimental animals and from patients pointing to the three points of similarity between the records from animals with known atrial fibrillation and the records from patients with absolute arrhythmia (arrhythmia perpetua) These three points of resemblance are (1) absolute ventricular arrhythmia (2) absence of *P* waves and (3) presence of irregular oscillations of the galvanometer string due to the fibrillary waves themselves

Lewis Thomas Auricular Fibrillation a Common Clinical Condition *Brit M J* November 27 1909 II 1528

Lewis also published convincing evidence of the frequent clinical occurrence of atrial fibrillation

It is well known that in the late stages of mitral stenosis and in cases of general cardio vascular degeneration the pulse is frequently continuously and extremely irregular The type of irregularity is remarkable in that in radial and cardiographic curves it defies analysis The nature of the arterial curves has given rise to the term pulsus irregularis perpetuus and it has been supposed that the rhythm of the heart producing it has its origin in the node of Tawara (hence the term nodal rhythm) The condition is extremely common

Facts are now at my disposal permitting of two conclusions

I That a rhythm arising in the neighbourhood of the node gives rise to a totally different clinical picture This conclusion is based upon a detailed examination (polygraphic and electrocardiographic) of a case of paroxysmal tachycardia in which it can be demonstrated that auricle and ventricle contract together This rhythm is a rare clinical phenomenon

II That the irregular pulse of mitral stenosis etc already referred to is due to fibrillation of the auricle

The second conclusion is based upon the following evidence

"1 The clinical irregularity presented by arterial and heart apex curves is unique The rhythm is entirely disorderly and the sizes of the beats do not correspond to the pauses which precede them Fibrillation of the auricle results in a

similar action of the ventricle and its action under these circumstances is unique experimentally

2 Electrocardiograms taken from patients exhibiting the irregularity show a number of irregular waves apart from the ventricular curve they are more clearly defined in diastole They are found in no other disorder of the heart s action They disappear when in a paroxysmal case the irregularity vanishes and are therefore due to a temporary and disorderly action of some part of the heart wall Cardiographic curves give no evidence of such a disordered action in the ventricle Fibrillation of the auricle yields curves which are identical in every respect and no such curves have been obtained by any other experimental means Further the waves on the experimental electrocardiograms can be shown to correspond to the fibrillary movements in the auricle by means of synchronous tracings

"3 The venous curve in the clinical irregularity is of the ventricular type all the prominent waves occur during ventricular systole and there is no wave corresponding to a normal auricular contraction The same statement applies to the venous curves in fibrillation of the auricle The clinical and experimental curves are of the same nature

Incidence Atrial fibrillation is common ranking probably third in frequency as a disturbance of rhythm premature beats and atrial paroxysmal tachycardia ranking first and second Most statistics especially hospital figures indicate that atrial fibrillation is more common than paroxysmal tachycardia but this is almost certainly due to the fact that atrial fibrillation is a striking disorder usually permanent and easily recorded graphically while paroxysmal tachycardia is a transient disorder often overlooked or scarcely heeded and difficult to record graphically because of its short duration Atrial fibrillation even of paroxysmal type rarely escapes notice and almost without exception comes eventually under medical scrutiny In a group of 3 000 patients with cardiac symptoms or signs analyzed in New England (White and Jones 1928) 376 or 12 5 per cent were found to have atrial fibrillation 309 (82 2 per cent) of which were permanent and 67 (17 8 per cent) paroxysmal in type

Mechanism (abnormal physiology) Absolute irregularity of the action of the heart termed in the past delirium cordis and absolute or perpetual arrhythmia was attributed at first to a variety of different mechanisms among them atrial paralysis with idioventricular rhythm atrioventricular nodal rhythm controlling both atria and ventricles and the conflicting activity of multiple incoordinated abnormal atrial pacemakers Then for many years it was widely believed that the condition is due to the establishment of a wave of excitation and contraction constantly circulating at a more or less irregular but very rapid rate about a more or less irregular and variable ring of muscle in the atria chiefly about the great veins giving off stimuli to the rest of the atrial muscle and to the ventricles the ventricles responding as rapidly as they can but at an irregular rate (Lewis 1921) This conception was based on fundamental observations of the circus movement of muscular contraction waves in experimental animals (Mayer 1908 Garrey 1912–1914 Mines 1914) It was shown that a contraction wave may continue to circulate around

a band of muscle if such a band is long enough to allow the point of origin of the wave to recover from its refractory (nonresponsive) stage by the time the circulating wave reaches it again and that such a circus wave can apparently be established in the dog s atrium by a rapid series of faradic stimulations The circus wave has been thought to be the underlying mechanism of both atrial flutter its simplest manifestation and atrial fibrillation, its more complicated form Recently however this theory of the circus movement has been challenged and another mechanism namely that of excessively rapid atrial discharge of stimuli from one atrial focus, proposed in its place (Scherf et al 1948 Prinzmetal et al 1949) The flutter waves have been clearly visualized by the use of slow motion pictures and have been seen to travel in all directions from an irritated focus and not in the form of a circus also it has not been stopped by a burn placed across a circus path (Prinzmetal et al 1949) Thus this new explanation of flutter and fibrillation of the atria relates them closely to the mechanism of ordinary paroxysmal tachycardia the difference being simply that of rate However several difficulties remain to be explained including the rarity of atrial rates between those of flutter and of paroxysmal tachycardia the electrocardiographic differences and finally the clinical dissimilarities More studies of this problem are obviously needed

The rate of initiation of the excitation and contraction wave in the atrial muscular tissue in atrial fibrillation is very rapid averaging in man about 400 per minute and varying between 300 and 500 The speed is so great that areas of block or refractory points develop accounting for the irregularity of rate seen in the electrocardiogram as regards both atrial and ventricular action Related to this same mechanism is that found in atrial flutter where the excitation occurs at a slower and much more regular rate (though not always absolutely regular) at 200 to 400 per minute averaging 300 Transitional stages between fibrillation and flutter are common at atrial rates of about 350 and they have been variously called impure flutter flutter fibrillation and 'coarse fibrillation the last term referring to the coarse atrial deflections seen in the electrocardiogram a halfway stage between the wide regular oscillations of flutter and the fine irregular movements of fibrillation (Figure 158) A new term auricular tremulation has been suggested for this intermediate stage (Pinchenzon 1937) but it seems unnecessary to multiply designations for the mechanism responsible for both atrial fibrillation" and atrial flutter

The ventricular response to the very abnormal atrial mechanism in atrial fibrillation is almost invariably grossly irregular and rapid when first encountered at about 130 to 150 per minute before therapy has been instituted and in the absence of organic or functional heart block Heart block either permanent from disease or temporary from the functional effect of drugs reduces the ventricular rate but does not control the ventricular arrhythmia unless the block is rendered complete

It is of interest to observe that in spite of the loss of sinoatrial control of

the heartbeat outside influences can still affect the heart (ventricular) rate when there is atrial fibrillation apparently through the action of the vagus and sympathetic nerves on the atrioventricular node and bundle thus excitement and exertion will increase the heart rate and changes in rate with respiration are often seen especially in sensitive nervous persons with neurocirculatory asthenia In rare instances the ventricular rate may be controlled by ventricular

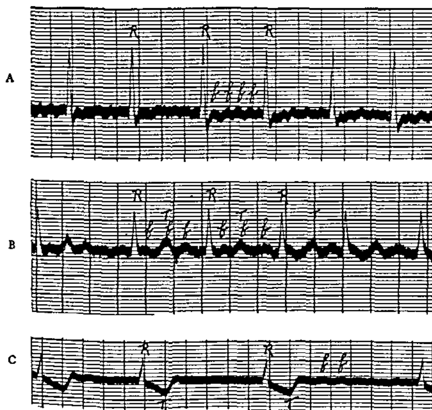


FIG 158 Electrocardiograms (Lead 2) showing atrial fibrillation (*A*) Fine" type with high rate of atrial action (*B*) coarse" type with slow rate of atrial action (*C*) atrial fibrillation with considerable degree of atrioventricular block (ventricular rate below 60) and inverted *T* waves (digitalis effect)

pacemakers in spite of the presence of atrial fibrillation This happens in three conditions (1) complete heart block (2) ventricular paroxysmal tachycardia and (3) ventricular escape or idioventricular rhythm superimposed on partial block when for some reason as from digitalis stimulation the atrioventricular node becomes sufficiently irritable to control the ventricular action at regular rates of moderate speed usually about 60 to 90 per minute

Ectopic contractions arising in the ventricle also often interrupt the arrhythmia induced by atrial fibrillation this is most strikingly seen when every beat of supraventricular origin is followed by a premature beat to produce the

so-called bigeminal or coupled pulse characteristically found with digitalis intoxication It is of interest to note that in such cases the ectopic or premature ventricular beats are always evenly spaced after the preceding beats of supraventricular origin even though the pairs occur irregularly The explanation of this regular interval between the first and second beats of the couples in the bigeminal rhythm of atrial fibrillation is not certain, but it is probably due to re-entry of the normal beat at some point of local block or prolonged refractory period the muscle failing to respond at that point to the original stimulus but able finally to contract and to start a new heartbeat in adjacent muscle (which has recovered from its own refractory phase) when the original stimulus reaches it by a circuitous route

The speed length and points of block (or refractory state) of the flutter wave in the atria determine its existence as flutter or as fibrillation Certain factors particularly two drugs influence these conditions

Digitalis tends to cause intra atrial block by increasing the refractory period through its direct action on the atrial muscle but its usual chief effect is to increase the rate and irregularity of the excitation wave and to shorten or hasten its course by decreasing the refractory period of the muscle through vagal action this vagal action overrules the direct effect on the muscle In this way digitalis acts to convert atrial flutter into atrial fibrillation and sometimes this is followed by a return of normal rhythm Digitalis while increasing the atrial rate practically always slows the ventricular rate in atrial fibrillation by increasing the grade of atrioventricular block except in rare cases when massive doses may cause a regular idioventricular rhythm or ventricular paroxysmal tachycardia

Quinidine sulfate slows the excitation wave (more effectively than quinine) by increasing the refractory period of the atrial muscle at the same time that it increases its duration this increase in duration probably is necessary for the continuance of the atrial action which otherwise would always be quickly stopped (as it sometimes is) by the increase in the refractory period The depressant and paralyzing action of quinidine on the vagus nerve acts to reenforce the direct effect of quinidine on the atrial muscle The excitation wave takes a slower and more regular course under the effect of the quinidine This drug has therefore a tendency to convert atrial fibrillation into atrial flutter It also tends to increase the ventricular rate when the atrial rate falls If the increase in the refractory period of atrial muscle under quinidine therapy is so great that it overbalances the longer duration of the excitation wave the latter may be unable to continue and the abnormal mechanism abruptly ceases. When at such a time the sinoatrial or rarely the atrioventricular node resumes action a regular heartbeat results but if both of these nodes are themselves depressed by the drug the heart may cease action altogether a probable explanation of death that has occurred in a few cases under quinidine treatment when embolism was not responsible

Thus the atrial rate may be increased in rate by digitalis from under 300 per minute to over 500 while the reverse is the effect from quinidine Even

though the usual experimental data and theoretical considerations indicate that digitalis and quinidine may act in opposite ways on the refractory period of the atrial muscle and thereby cause opposed effects clinical experience has shown that often it is worthwhile to digitalize before administering quinidine partly because normal rhythm is more readily restored thereby and partly because the ventricular rate is kept from rising too high when the rate of the atrial contractions is reduced by the quinidine It is also possible that fixed atrial flutter may be prevented by preliminary digitalization although of that there is as yet no proof

Finally it should be stated that atrial fibrillation is by no means a constant or perpetual condition as was at one time thought it is frequently paroxysmal in nature although once established for a period of several weeks it does tend to persist

Etiology *Cause* The cause of the establishment of the abnormal mechanism of atrial fibrillation is often obscure In most cases there is an important grade or type of heart disease or an important toxic or disease process of other nature but sometimes there is no such cause the individual seeming perfectly healthy without heart disease or poisoning of any sort Thus the condition is fundamentally a functional disorder and not in itself to be classed as heart disease

Atrial fibrillation is attended usually by little or no myocardial degeneration or inflammation but nearly always an unusual degree of strain or nervous excitability exists Mitral stenosis and thyrotoxic heart strain are the two cardiac conditions relatively most often associated with atrial fibrillation hypertension and coronary heart disease are only occasionally complicated by this arrhythmia Aortic valve disease congenital defects syphilitic aortitis and bacterial endocarditis are uncommonly associated with atrial fibrillation probably because the atrial strain and nervous stimulation are less The mystery of the rarity of atrial fibrillation in subacute bacterial endocarditis may be explained by the fact that this infection only infrequently attacks mitral valves that are badly stenosed and that it selects rather the aortic valve and slightly deformed mitral valves from which defects there is little or no atrial strain Atrial fibrillation is more common when the left atrium is under strain or enlarged no matter what the cause of the enlargement than when it is of normal size the commonest causes of such strain and enlargement are mitral valve deformity (especially stenosis) and failure of the left ventricle due to hypertension myocardial infarction or advanced aortic valve disease

Once upon a time it was customary to label any individual over the age of fifty years who showed atrial fibrillation and nothing else wrong as an arteriosclerotic (meaning coronary) cardiac victim but now it is realized that such designation is unjustified it is perfectly true that cardiac arrhythmias like gray hairs are more common with increasing years and that a less adequate coronary circulation may be somewhat responsible but by and large even in older persons it is wiser in the absence of other evidence to regard atrial fibrillation as a disorder of function rather than as a sign of heart disease

Noncardiac etiologic factors responsible occasionally for atrial fibrillation either in paroxysms or in established form are poisoning by toxic agents of all sorts such as excessive use of tobacco and alcohol especially in unaccustomed amounts on an occasional spree gas poisoning food poisoning and infectious diseases (like pneumonia) Sometimes violent exertion and excitement, trauma and surgical operations (especially of the thorax) are responsible for the onset of paroxysmal or permanent atrial fibrillation with little or no heart disease In a group of 49 cases of atrial fibrillation without heart disease reported by Orgain Wolff and White (1936) the exciting factors responsible for the onset of atrial fibrillation (paroxysmal or permanent) were apparently pneumonia malarial chill pelvic abscess burns surgical operation ether alcohol gallbladder colic vomiting exertion, and emotion (excitement and fear)

Finally there appears to be some sort of susceptibility or nervous hypersensitiveness that predisposes to this abnormal mechanism Several members of one family may be affected even in youth, without serious disease and in fact in some cases without any evident disease at all

In an analysis of 575 consecutive cases of atrial fibrillation reported by McEachern and Baker (1932) the chief etiologic relationships were as follows rheumatic heart disease 34 4 per cent coronary disease and old age 31 1 per cent hypertension 16 9 per cent thyrotoxicosis 7 5 per cent emphysema 5 0 per cent syphilis 3 0 per cent and miscellaneous 2 1 per cent In the series of 376 cases of atrial fibrillation reported by White and Jones (1928) 346 patients had definite evidence of organic heart disease while 30 (8 per cent) were apparently free from heart disease Almost half 158 (45 6 per cent) of the organic group of 346 cases belonged to the rheumatic type with or without complications Seventy four (21 4 per cent) of the cases had coronary heart disease without other complications 15 (4 3 per cent) had hypertension alone while 92 others (26 6 per cent) had hypertension complicating other conditions and 14 (4 0 per cent) had thyrotoxicosis alone

Sex The sexes are unequally affected by atrial fibrillation paroxysmal and permanent It was stated in the second edition of this book that about twice as many males as females show this arrhythmia perhaps because men are generally subject to greater strain than are women a more recent review of 10 000 cases which included 645 patients (6 45 per cent) with atrial fibrillation electrocardiographed at the Massachusetts General Hospital from January 3 1939 to February 6 1942 showed a ratio of 71 per cent males (455 cases) to 29 per cent females (190 cases)

Age Atrial fibrillation is very rare in infancy and early childhood uncommon in adolescence but increasingly more frequent in each decade of life as is generally true in the case of all other disorders of heart rhythm Of the 575 cases of atrial fibrillation reported by McEachern and Baker (1932) 0 5 per cent were under ten years of age 4 2 per cent ten to twenty years old 5 4 per cent twenty to thirty 15 0 per cent thirty to forty, 20 2 per cent forty to fifty 26 1 per cent fifty to sixty 20 5 per cent sixty to seventy 7 8 per

cent seventy to eighty and 0 3 per cent eighty to ninety Despite the falling off *in the figures of absolute incidence in the last three decades of life* atrial fibrillation actually continues to increase in frequency relative to the rapidly decreasing number of persons surviving to advanced age

Pathology There is no pathologic change characteristic of atrial fibrillation There may or may not be organic heart disease usually there is There may or may not be myocardial abnormality other than hypertrophy usually there is not Extensive heart disease myocarditis and myocardial degeneration may *exist without atrial fibrillation The atria are usually enlarged (dilated) in* atrial fibrillation and their walls may show areas of degeneration and fibrosis which however are neither uniform nor specific

Symptoms Atrial fibrillation especially if it is of permanent nature and properly treated may exist without any symptoms Usually however the patient is aware of the irregular heart action which he describes variously as fluttering irregular palpitation or pounding skipping or tumultuous action This *consciousness of the abnormal heart action is particularly marked during* paroxysms of atrial fibrillation and at the time of the onset of permanent atrial fibrillation before the ventricular rate has been controlled At such times the distress nervous irritation and fear or worry may be so great that the patient feels and may even be thought to be far sicker than he is He may be greatly distracted with the thought of impending death and a feeling that his heart must burst or stop after its vigorous leaping about Even after full reassurance much discomfort *usually persists and although the fear is gone complete or* partial invalidism may come with every paroxysm of atrial fibrillation or may persist if the paroxysms occur frequently or if the arrhythmia becomes permanent Gradually after the patient becomes accustomed to the recurrent paroxysms or to the constant arrhythmia especially if the ventricular rate is controlled by treatment the symptoms decrease and as a rule finally disappear entirely

Palpitation is the characteristic symptom of atrial fibrillation Dyspnea and pain are much less common but they may develop as a part of neurocirculatory asthenia if there is an associated marked psychic element (from fear and nervous exhaustion) dyspnea may set in if myocardial fatigue or pulmonary engorgement due to mitral stenosis develops as the result of the rapid irregular heart action or the distress of an angina pectoris may appear due to extra work imposed by rapid heart action on a myocardium very badly supplied with blood Other symptoms of the frequent complication of congestive failure are occasionally seen The rarity of the association of atrial fibrillation with angina pectoris is an interesting problem best explained by the limitation of activity that occurs with atrial fibrillation because of palpitation dyspnea fear or medical advice there being no longer enough strain on the myocardium to exceed the reserve of the limited coronary circulation When the heart action is very rapid in atrial fibrillation there may be weakness dizziness and faintness due in part at least to cerebral anemia As in the case of paroxysmal tachycardia syncope may rarely occur at the end of a paroxysm

of atrial fibrillation due to failure of the normal pacemakers of the heart to resume action at once

Signs The characteristic sign of atrial fibrillation is absolute irregularity of the beating of the heart whether the rate is rapid or slow Although this sign is not absolute proof of atrial fibrillation there are very few exceptions (gross sinus arrhythmia multiple premature beats and atrial flutter with varying grades of heart block) Graphic records are useful in confirming the diagnosis of atrial fibrillation but they are usually unnecessary so far as this one particular finding is concerned a phlebogram will show atrial fibrillation but an electrocardiogram is of more value since it gives other additional information for example the effect of digitalis on the *T* waves (Figures 152 page 832 and 158C page 897) and the state of the coronary circulation

Often when the patient is first seen before treatment is started the heart action may be so rapid irregular and weak that some beats fail to cause pulsation in the peripheral arteries, as a result the apex rate is faster than the radial pulse rate and the difference is called the pulse deficit When the ventricular rate slows as the result of rest and digitalis the heart action becomes steadier stronger and more regular fewer beats or none fail to reach the wrist until finally with a slow heart rate the pulse deficit entirely disappears although of course the atrial fibrillation itself persists The apex rate at first may be as high as 150 per minute and the radial pulse rate as low as 100 with a pulse deficit of 50 later after full digitalization both apex and radial rates may be 75 with no pulse deficit at all the radial rate sometimes actually rises with improved strength of pulse as the heart rate slows Generally at the onset the radial pulse rate is high as well as the apex rate and both drop with treatment (Figure 151 page 829) Although with training in palpating the pulse less deficit is found in cases of atrial fibrillation with rapid ventricular rate than before such training nevertheless there often is an appreciable deficit at fast rates and to chart carefully several times a day the amount of pulse deficit along with the apex rate is one of the best ways to follow the effects of treatment The observer usually a nurse must be taught in such cases to record not only the radial pulse rate but what is much more important the apex heart rate also This procedure used to be neglected at times even in good hospital clinics or in private practice and as a result there used to be considerable uncertainty about the course of the true heart rate of these cases but in recent years this difficulty has been largely eliminated

There may be no other signs of the abnormal atrial mechanism than the absolute irregularity of the heartbeat and the electrocardiographic evidence Usually however there is some cardiac enlargement due to the presence of some sort of heart disease this may be great or little or primarily of left ventricle of right ventricle or of the atria (especially of the left atrium in mitral stenosis) Murmurs may or may not be found if present they are due most commonly to mitral stenosis or to cardiac dilatation There may be signs of congestive heart failure or of constrictive pericarditis

The blood pressure may be normal low or high with atrial fibrillation

Often hyperpiesia is present and this important condition may be missed if the blood pressure is not measured Because of the difficulty of obtaining accurate figures of blood pressure in the presence of atrial fibrillation especially with rapid ventricular rate due to the greatly varying force of successive beats sphygmomanometry was at one time largely abandoned in cases of atrial fibrillation or made very complicated by the use of special technic such as taking the digital pressure and comparing it with the usual brachial standards or calculating the average brachial pressure by a fractional method As a matter of fact clinical experience in hundreds of cases has shown the feasibility and relative reliability of taking the blood pressure in the routine way in cases with atrial fibrillation Although there is more or less variation in pressure of beats a sufficiently accurate average can be quickly determined in a rough manner for both systolic and diastolic pressures These pressure readings usually correspond quite closely to those of the same cases during normal heart rhythm either before or after the atrial fibrillation Moreover when the ventricular rate is slowed by digitalis the beats become much more uniform in force and may vary very little or not at all on blood pressure estimation therefore if one is in doubt about the pressure in a difficult case sphygmomanometry can easily be repeated after the heart rate has been slowed or normal rhythm restored Weak beats have a smaller pulse pressure with lower systolic and higher diastolic levels

Roentgen ray study is not usually of much help although it is always essential to make such a study an integral part of a thorough examination of every patient with cardiac symptoms or signs The ventricular arrhythmia is often evident fluoroscopically but it is less easily analyzed by roentgen ray than by auscultation or electrocardiography The abnormal atrial mechanism is generally indistinguishable by roentgen ray the atria appearing to partake only of the ventricular movement Abnormalities of cardiac size and shape if pronounced are of course easily made out roentgenologically and may help with the finding of atrial fibrillation to establish such a diagnosis as mitral stenosis

Electrocardiography is of the greatest assistance in confirming the diagnosis of atrial fibrillation although this confirmation is often unnecessary Electrocardiography is still more useful in showing the presence or absence of associated abnormalities like bundle branch block and in following the effect of digitalis therapy on the *T* wave or of quinidine treatment on the atrial mechanism The oscillations caused by the excitation wave in atrial fibrillation are usually best made out in Lead 2 but sometimes they are maximal in Lead 3 Precordial leads over the ventricles are usually disappointing but if the exploring electrode is placed over the right atrium just to the right of the sternum in the position of the first of the six routine precordial leads that is in the fourth intercostal space or better still in the third intercostal space just at the right of the sternum the site of the so called special atrial lead point (or over the left atrium esophageally) the *f* or fibrillation waves may be very evident

Course and prognosis Atrial fibrillation may be of trivial importance or it may be very serious If it occurs in the form of transient paroxysms in a person

without heart disease it may be disagreeable but nothing more recurring off and on at longer or shorter intervals or perhaps only once or twice without recurrence Untreated paroxysms of atrial fibrillation usually last a few hours, with ordinary limits of a few minutes to several days and very rarely extreme limits of a few weeks or months or even years (Fogel 1943) Even if it occurs in permanent form atrial fibrillation may cause little or no disability if there is no important heart disease and if the heart rate is kept reasonably slow by constant digitalis therapy or controlled by organic heart block without drugs Cases have been known with a history of paroxysmal or of permanent atrial fibrillation over periods of many years even thirty or more Paroxysms may occur only once or twice and be followed by long intervals of freedom for many years or they may recur frequently at intervals of months or weeks and yet not cause disability or more than passing discomfort if the heart is strong.

In general atrial fibrillation like premature beats and paroxysmal tachycardia is a functional disorder that in itself is a far less serious factor in crippling or in shortening life than is the underlying heart disease or other condition that may be present provided that either the atrial fibrillation is transient or the ventricular rate is controlled by treatment. Now that quinidine therapy is successful in restoring normal rhythm in a good many cases of permanent atrial fibrillation this type of atrial fibrillation can sometimes be transformed into that of paroxysmal nature with long intervals of months or even many years of freedom from any disturbing cardiac arrhythmia. Long lives of full activity may thus be carried on through the proper use of quinidine and digitalis in spite of the occasional occurrence of temporary disturbing paroxysms of atrial fibrillation or of the presence of permanent atrial fibrillation

Complications. Unfortunately atrial fibrillation cannot always be regarded in so optimistic a way as that expressed above Since it so often complicates very serious heart disease its occurrence may precipitate heart failure and even death unless successful therapy is quickly instituted It is always something of a burden even to a normal heart though in such cases the cardiac reserve is sufficient to take care of the disorder The tachycardia rather than the arrhythmia is the serious factor and if that is reduced to a normal heart rate the circulation may be maintained in a satisfactory way in spite of the irregularity The fact however that the circulation is more efficient with normal rhythm than with atrial fibrillation at the same heart rate makes it often worthwhile to attempt the restoration of normal rhythm for there may come a time in an individual case when the more economic circulation maintained by normal rhythm means the difference between cardiac sufficiency and cardiac failure Although long-continued uncontrolled atrial fibrillation alone may in rare cases cause a normal heart muscle to fail the ordinary case of heart failure caused by atrial fibrillation is one showing extensive heart disease especially mitral stenosis Proper treatment by digitalis and rest may prolong life for a number of years probably sometimes for as many as ten or twelve but finally there comes a time often at about forty five to fifty years of age when

with advanced mitral stenosis the heart reserve can no longer be maintained and death comes in spite of the best treatment The early recognition and early and persistent treatment of the atrial fibrillation which appears as a com plication of heart disease is of great importance in prolonging life and reducing disability in cardiac cripples

There is one condition thyrotoxicosis in which atrial fibrillation either in paroxysmal or permanent form is especially likely to be the earliest sign of cardiac strain If the thyrotoxicosis is not corrected the atrial fibrillation may become established and even eventually cause heart failure and death because the ventricular rate is difficult to control until the thyrotoxicosis itself is controlled It is important always to consider the possible existence of thyrotoxicosis in any case of atrial fibrillation of unknown cause that is with out sufficient pathologic change in the heart to account for it particularly if it is difficult to control the ventricular rate with digitalis

An important complication of atrial fibrillation besides heart failure is embolism into cerebral renal splenic or peripheral arteries causing hemi plegia of varying degrees and duration and other evidences of infarction the embolus coming from an intracardiac thrombus usually in the left atrium The stagnation of blood in the atria when they have ceased coordinate con traction favors the development of thrombi especially in the appendages pieces of these thrombi may break off and be precipitated into the blood stream more commonly in the systemic circulation less commonly in the pul monary circulation the emboli getting loose either during the fibrillation or at the time of the return to normal rhythm which occurs either spontaneously or as the result of quinidine therapy The complication of embolism in atrial fibrillation is infrequent but often serious and sometimes fatal

In very rare cases of mitral stenosis and atrial fibrillation there is formed free in the left atrial cavity a large spherical or ball thrombus which when it does occur partly occludes the atrioventricular ostium and may even tem porarily obstruct it to cause collapse of the patient a unique case with ball thrombus in the right atrium has been discovered (Wright et al 1944)

Sudden death is rare in atrial fibrillation its cause is not known although the onset of ventricular fibrillation has been suggested as responsible

Treatment The treatment of atrial fibrillation includes A that of the con dition itself and of its complications and B therapy directed to prevent parox ysms of absolute arrhythmia or recurrence of the atrial fibrillation if once abolished

A **The direct therapy of atrial fibrillation** varies somewhat with the condi tion of the individual patient

1 *Rest and digitalis* If there is congestive failure or very serious heart dis ease quinidine should only very rarely be used absolute rest should be enforced and full digitalization carried out as rapidly as necessary For an adult with atrial fibrillation who has not received digitalis or strophanthin and for whom emergency treatment is not needed digitalis leaf in 0 1 gm (1½ gr) pills may be given at the rate of one pill three times a day for 4 or 5 days or

0 06 gm (1 gr) three times a day for one week such a course to be followed by a ration of one pill daily of either dosage depending on the individual case constantly thereafter so long as the fibrillation persists This therapy should suffice to reduce the heart rate to normal by causing heart block and to keep it normal this dosage is an average amount and may have to be decreased or increased in individual cases For emergency therapy 0 4 gm (6 gr) of standardized digitalis in solution (e g Digifolin) may be given intravenously to be repeated in four hours and again in the same or smaller amount in eight more hours if necessary or Cedilanid 4 cc (0 8 mg) may be given by vein to be repeated in four hours or digitoxin 0 6 mg may be administered by mouth or vein and repeated in four hours or strophanthin (ouabain) 0 25 to 0 5 mg (1/240 to 1/120 gr) may be injected intravenously to be repeated in twelve hours if needed these measures should be followed by a daily ration of one 0 1 gm (1½ gr) or 0 06 gm (1 gr) digitalis leaf pill For further details of digitalis therapy see Chapter 30

2 *Quinidine therapy* A striking discovery concerned with the control of the functional atrial disturbance in fibrillation and flutter has been the therapeutic application of quinine and its isomer quinidine The effective use of quinine in the control of rebellious palpitation was first mentioned by Senac in 1749 and rediscovered a century and a half later by a patient of Wenckebach (1914) another alkaloid of the cinchona bark quinidine an isomer of quinine was found by Frey to be much more effective than quinine (1918) Although substitutes for commercial quinidine have been tried (see below) nothing more effective has been found as yet

If the patient with atrial fibrillation has had no congestive failure or serious heart disease or history of embolism he should be considered a possible candidate for quinidine therapy At least two thirds of all such patients can be restored to normal rhythm by this treatment and half of these somewhat more than one third of the original total number can maintain normal rhythm for at least several months sufficiently long to be considered definitely benefited by the therapy Some cases maintain normal rhythm for years even for ten years or more in a few cases with relief of symptoms and a return to normal active lives One of my patients has maintained normal rhythm for twenty five years having been one of the very first cases of persistent atrial fibrillation to whom I gave quinidine soon after its introduction to this country Successful quinidine treatment has been an important accomplishment in medical progress

The percentages of successful restoration of normal rhythm in series of patients reported in the literature vary widely from 7 to 94 per cent averaging about 60 per cent This wide variation is due in part at least to selection of cases and in part to dosage and other factors Two relatively recent reports give figures of 23 out of 34 cases (68 per cent) maintained for over three months in 16 (Laake, 1945) and 44 out of 50 cases (88 per cent) maintained in 20 for more than a month (McMillan and Welfare 1947) The more normal the heart fundamentally the more likely is quinidine to act

successfully and safely Hence it is particularly indicated when the arrhythmia is simply a very annoying disorder of function There are however cases who are dangerously ill in whom the drug can be lifesaving as for example (1) in restoring normal rhythm in a patient with congestive heart failure maintained by the tachycardia of his atrial fibrillation which is resistant to digitalis control the heart rate being lower during normal rhythm in such cases than during atrial fibrillation and (2) in reducing the likelihood of the deposition of further intra atrial thrombi which might become emboli in patients with atrial fibrillation who have already suffered from embolism contrary to the classical rules of quinidine therapy (White and Blumgart 1942)

The patient receiving quinidine in large dosage to restore normal rhythm should be under close observation preferably in bed and where electrocardiographic observations can be made so that the effect of the drug can be accurately followed and its toxic as well as its beneficial action noted Since quinidine in large dosage is a poison it must be used with care and by the exercise of care accidents and fatalities that have been reported in rare cases in the past can largely be avoided A good method of administration of quinidine that has been found effective is to give it by mouth in the form of the sulfate in tablets or powders of 0 2 gm (3 gr) each A test dose of a single tablet or powder may first be given to make sure that the individual is not unduly sensitive such sensitiveness is however very rare If no toxic symptoms (of cinchonism—see below) appear administration of the drug in large dosage can be begun Of various schedules of dosage two are as follows (a) 0 4 gm (6 gr) that is two tablets or powders every two hours for five doses for example at 10 A M 12 M and 2 4 and 6 P M making a total of 2 0 gm (30 gr) in the day continuing this regime for two or three days at a time if normal rhythm is not restored during the first day or on the following night but stopping the drug on the appearance of toxic symptoms normal rhythm or obstinate atrial flutter (of more than three days duration) in a few cases 6 or 7 or 8 doses of 0 4 gm (6 gr) each at two hour intervals in a day have succeeded when the five doses have not (b) 0 4 gm (6 gr) every four hours day and night except for the omission of one night dose during sleep, for a few days if necessary—the daily dose by this procedure will also equal 2 0 gm (30 gr) but this method is less reliable Sometimes smaller doses down to one half the amount noted above or larger doses up to several times the above mentioned amount (even 6 0 gm [100 gr] or more a day) have been given or recommended but it is probable that the methods outlined here are as satisfactory as any and better than most Massive doses of more than 4 gm (60 gr) of quinidine sulfate in a day are in general inadvisable and dangerous in the treatment of atrial fibrillation but when life is in jeopardy after prolonged ventricular paroxysmal tachycardia it is fair to take the risk of the larger doses (see Chapter 32)

In special emergencies or when the drug cannot be taken by mouth quinidine can be given intramuscularly or intravenously preferably the former because of the danger of toxic effects from rapid administration by vein It

can be given in the form of a solution of either the lactate the gluconate or the hydrochloride (injectable) in the dosage of 0 2 to 0 5 gm (3 to 7½ gr) and repeated at two hour intervals as needed and as tolerated On occasion, quinine dihydrochloride 0 5 gm (7½ gr) intramuscularly at two hour intervals has proved effective but in general for the treatment of cardiac arrhythmias quinine is inferior to quinidine

So soon as toxic symptoms (cinchonism) of any important degree develop —marked tinnitus deafness, urticaria nausea vomiting diarrhea intraventricular block (ascertained by electrocardiogram), and very rapid regular heart action—the drug should be discontinued Observation of the patient should always be made for toxic drug effects before the administration of each new dose and electrocardiograms should be taken several times during the day routinely at least after every other dose or even oftener An increase in ventricular rate is natural during quinidine therapy although it is not always encountered when the atrial rate falls, atrioventricular conduction improves so that the ventricular rate rises and atrial and ventricular rates tend to approach a common level therefore even if a tachycardia develops it need cause no concern if it does not exceed 130 or 140 if it rises higher the drug should be discontinued for either the tachycardia may produce a very disagreeable palpitation or it may mean that there has developed a dangerous toxic heart rhythm such as ventricular paroxysmal tachycardia An unusual toxic manifestation of the oral use of quinidine sulfate—high fever—has been reported (Sturnick 1942)

If normal rhythm appears the large doses of the drug should be reduced to daily rations for a shorter or longer interval as desired for example one 0 2 gm (3 gr) tablet three or four times a day for a few weeks or the quinidine sulfate may at once be discontinued altogether If however the drug is continued every day for many months it tends eventually to lose its effect or it may cause annoying tinnitus deafness or looseness of the bowels so that occasional periods are to be recommended in which the drug is withheld altogether for a few days or a few weeks if possible Much judgment is necessary in dealing with an individual case and experience with that case must control the therapy In fact the patients themselves often become expert in handling the situation and are then better able to arrange time and amount of doses of quinidine than are their physicians For example patients may find that they do not need the drug except at certain times during or just before some particular effort against which they require special protection for their heart for a few hours or a few days In such instances the quinidine should be taken by mouth about 1½ hours before the particular strain that tends to cause th atrial fibrillation The effect of a dose of quinidine sulfate given by mouth reaches its height in 1 to 2 hours and ceases in 4 to 5 hours

If persistent atrial flutter appears it is best to stop the quinidine and to resort to digitalization to attempt to control this difficult disturbance of rhythm Atrial flutter is a natural transitional stage in the change from atrial fibrillation

to normal rhythm but it is usually brief and often too transient to be recorded electrocardiographically

Serious accidents can happen during quinidine therapy but they are very rare and in carefully selected cases very unlikely They include embolism due to pumping out by the heart of bits of intracardiac thrombus on restoration of normal atrial action Embolism can however occur with persistent atrial fibrillation alone and in fact does so then as often as upon the return of the heart to normal rhythm Sudden death without embolism has also been noted in several cases during quinidine therapy and the cause has been variously explained by respiratory paralysis cardiac paralysis ventricular fibrillation or other mechanism Cardiac standstill is the most likely explanation being due to the paralysis of both pacemakers of the heart in the sinoatrial and atrioventricular nodes as the result of the toxic effect of the quinidine when these nodes are depressed and the abnormal mechanism of atrial fibrillation is brought to an end by the drug there may be no available pacemaker to take up the function of exciting the heartbeat death resulting The finding of atrial standstill in two cases in which atrial fibrillation was abolished by quinidine has been noted by Wolff and White (1929) fortunately in these cases the atrioventricular node excited regular ventricular beats until the atria recovered their activity

Digitalis may or may not be used with the quinidine in the attempt to abolish atrial fibrillation It seems to be helpful and is generally to be recommended though it is not always necessary It may be used in the dosage of 0 06 gm (1 gr) of digitalis leaf or 0 1 mg of digitoxin three or four times a day for five to seven days

If normal rhythm is not restored by quinidine sulfate in the course of two or three days the drug should be discontinued and full digitalization should then be established and maintained if it has not already been accomplished After a short interval of one to several weeks a second course of quinidine sulfate just like the first may be administered if desired and if that too is unsuccessful even a third course may be given later after another interval perhaps of a few months and with some variation of dosage If digitalis is not used with the quinidine during an unsuccessful course it may be tried with the next course It is of interest and importance to note that occasionally a second or third course or a larger dosage of quinidine sulfate has proved successful *after early attempts have failed*

In successful quinidine therapy normal rhythm is generally restored after a few doses on the first or second day of a course of the drug infrequently atrial fibrillation may be banished by the single test dose or after the first regular dose of the course Normal rhythm usually persists after its restoration for at least several weeks or months and sometimes for years If atrial fibrillation recurs it should be treated again in the same way as at first but if it recurs often and normal rhythm lasts repeatedly for only a few hours days or weeks it is best to abandon further quinidine therapy and to establish and

maintain digitalization In such cases digitalization usually supports a satisfactory circulation and keeps the patient in a good enough state of health without the bother of frequent courses of quinidine and the annoyance of frequent shifting of the heart beat from normal rhythm to atrial fibrillation and back again However not infrequently digitalis and quinidine are helpfully given together the former to help to maintain an improved myocardial tone and to prevent much tachycardia when atrial fibrillation occurs and the latter to reduce the frequency of paroxysms of atrial fibrillation or to prevent them altogether

3 *Other measures of treatment of atrial fibrillation* are of less importance than is the use of digitalis and quinidine nevertheless some measures are useful and often necessary Avoidance of unnecessary physical and mental strain fatigue infections overeating and intemperate use of tobacco tea coffee and alcohol (small amounts of these are often permissible) should always be a matter of routine even though the atrial fibrillation is the only abnormality The more trouble of other sort there is especially in the form of heart disease and failure the greater naturally must be the limitation imposed on the patient Exercise if possible should be encouraged in mild form especially walking but it is to be remembered that although the heart rhythm no longer originates in the sinoatrial node the heart rate is still subject to outside influences apparently through nerve action on atrioventricular conduction Excitement and exertion will increase the heart rate in spite of digitalis even more than is the case in normal rhythm

Special restrictions and special diets for atrial fibrillation are unnecessary Other drugs than quinidine and digitalis are also as a rule unnecessary Synthetic quinidine and dihydroquinidine are effective but not superior to commercial quinidine while quinine is much less effective (Alexander et al 1947) strophanthus squill apocynum and convallaria may be effective in the manner of digitalis but they are inferior members of the digitalis group except in the case of strophanthin or ouabain which is more potent than is necessary and may be actually dangerous if given in large or often repeated doses—its use is much better limited to emergency treatment of congestive failure

In recent years two other drugs have been introduced as substitutes for quinidine in trying to abolish atrial fibrillation fagarine from South America (Deulofeu et al 1945 Taquini 1947 Scherf et al 1949) and atabrine (Gertler and Yohalem 1949) both have been effective to some degree but need further study incidentally fagarine can cause serious ventricular irritation

Symptomatic treatment and the therapy of complications or of other conditions associated with atrial fibrillation should be carried out with little or no regard to the arrhythmia

Surgical operations and anesthesia should not be withheld when they are obviously necessary procedures the atrial fibrillation is not a contraindication to their execution although it is always wise to control the heart rate or the

arrhythmia first by the use of digitalis or quinidine It is essential to remember that thyrotoxicosis is an important cause of atrial fibrillation and that it may be difficult or impossible to control this arrhythm a until the thyrotoxicosis itself is corrected either surgically or medically It has been also of much interest with thyrotoxicosis present to observe the calming influence on the heart rate either in normal rhythm or in atrial fibrillation of the administra tion of iodine for a short time in preparation for operation (for example 5 gr of potassium iodide or 5 drops of Lugol s solution three times a day for a week) The discovery of this effect was made accidentally by Trousseau many years ago (1863) when he gave by mistake a prescription for tincture of iodine instead of tincture of digitalis to a patient with thyrotoxicosis and tachycardia The heart rate was reduced much more readily by the iodine than by the digitalis which was later substituted on discovery of the original error

For the discomfort due to the palpitation induced by atrial fibrillation either in paroxysmal or in permanent form various medicines may be helpful in particular bromides (for example 1 gm [15 gr] of the triple bromides in solution two or three times a day for a few days as needed) Codeine and morphine should rarely be employed and then only to tide over some excep tionally severe period of palpitation and associated discomfort or pain espe cially when the tachycardia produces pulmonary edema or the status angi nosus before digitalis or quinidine becomes effective Since paroxysmal atrial fibrillation is commonly recurrent there is a real danger of habit formation (morphinism) in the use of the opiates

B **Therapy directed to prevent paroxysms of atrial fibrillation or recur rence of "permanent' arrhythmia** is much like that already outlined for the prevention of paroxysms of tachycardia in Chapter 32 In the first place factors that irritate the heart or nervous system and favor the onset of atrial fibrillation should be prevented or at least reduced to a minimum such factors include nervous excitement and fatigue sudden violent effort prolonged ex hausting exertion hearty meals excess of tobacco alcohol tea or coffee worry and late hours Secondly there may be conditions of ill health which favor the appearance or persistence of atrial fibrillation such as focal infec tions general diseases local strain of muscles or joints painful conditions like stones in kidney or gallbladder and heart failure These conditions should be corrected so far as possible but not too abruptly or vigorously Thirdly there is more or less specific therapy possible by the administration of quinidine sulfate in daily rations of 0 2 to 0 4 gm (3 to 6 gr) once twice three or four times a day according to need constantly for a few doses or for days at a time Often such quinidine therapy is successful at least in reducing the num ber and duration of the paroxysms of atrial fibrillation even if not in completely preventing them It is a common experience that patients who have numerous long paroxysms each lasting twelve to twenty four hours or more and coming as often as once or twice a week find that the attacks become infrequent and short under quinidine therapy lasting but two or three hours each time and coming perhaps once or twice a month Finally when quinidine sulfate rations

are ineffective it is wise to try the effect of digitalization and its maintenance In rare cases digitalis seems to reduce the number and duration of the paroxysms but its chief advantages lie in the facts (1) that when atrial fibrillation does occur depression of atrioventricular conduction already exists as the result of the digitalis effect and so the ventricular rate rises less than without digitalization and (2) that digitalis tends to maintain atrial fibrillation as a permanent disorder of rhythm after it has recurred paroxysmally and so with its simultaneous control of the ventricular rate permits a much pleasanter existence than when atrial fibrillation is constantly coming and going Sometimes quinidine and digitalis may be combined successfully in preventive therapy but if in spite of these drugs there is much discomfort from recurring attacks of atrial fibrillation other medicines especially the bromides or phenobarbital may prove useful in reducing the distress The bromides should be used cautiously to avoid a toxic effect

Protection of the heart from disturbing arrhythmias during surgical operations on and about the heart has been accomplished by the preoperative use of quinidine sulfate and the administration of procaine to the exposed heart or by intrapericardial injection but the degree of effectiveness of these procedures has not yet been fully determined In lung surgery too quinidine given preoperatively may prevent arrhythmias

Reassurance so far as the atrial fibrillation is concerned is almost always an important part of the therapy but the significance of the condition must not be minimized to the extent that the patient neglects necessary treatment.

Differential diagnosis Atrial fibrillation has to be differentiated from gross sinus arrhythmia multiple premature beats paroxysmal tachycardia and atrial flutter The most important point in differentiation of atrial fibrillation from any of these other disturbances of rhythm is the absolute irregularity of its rhythm which is almost invariably present and rarely simulated by any other condition If one is in doubt resort may be had to exercise or to the increase in rate produced by amyl nitrite or atropine such procedures usually abolish the arrhythmia of sinoatrial or premature beat origin and increase that of atrial fibrillation Besides differing from atrial flutter and paroxysmal tachycardia in rhythm atrial fibrillation differs from these disorders further in that it is more often a permanent and less often a paroxysmal state and in that it more often occurs with definite indications of organic heart disease also it more readily responds to quinidine and digitalis therapy

ATRIAL FLUTTER

Atrial flutter due to a disorder of atrial mechanism closely related to that of fibrillation but usually with regular rapid ventricular action is uncommon it was named by Jolly and Ritchie in 1911

Incidence Atrial flutter is probably not so rare as statistics indicate since shorter paroxysms may easily be missed or considered to be paroxysmal tachycardia in the absence of graphic records When it is recognizable without

graphic records atrial flutter is found only about twice to every fifty cases of atrial fibrillation When electrocardiograms are routinely taken atrial flutter is found about once for every 14 cases of atrial fibrillation Thus we found 104 cases of atrial flutter and 1 422 cases of atrial fibrillation among 10 000 patients electrocardiographed at the Massachusetts General Hospital from 1914 to 1931 (White and Sprague 1931)

Mechanism (abnormal physiology) Atrial flutter is characterized by regular but abnormal atrial contractions at a very rapid rate and usually by regular ventricular contractions at one half the atrial rate The atrial rate ranges from 200 or slightly less to 400 or slightly more with an average of 300 per minute The ventricular rate is often exactly one half the atrial rate because of 2 to 1 atrioventricular block sometimes it is slower than that or irregular due to greater or varying grades of block and rarely it is the same as the atrial rate due to the absence of block this last mentioned state often being called 1 to 1 rhythm Generally conduction within the ventricles themselves is normal but with very rapid rates functional intraventricular (bundle branch) block may occur disappearing later when the rate falls or the atrial flutter stops Very rarely complete heart block may be associated with atrial flutter

The mechanism of atrial flutter is not yet perfectly clear Like atrial fibrillation flutter has been for many years ascribed to a circus movement (Lewis et al 1920) but recently doubt has been cast on this mechanism as noted earlier in this chapter (Scherf et al 1948 Prinzmetal et al 1949) (see page 896) and an alternative proposed of rapid excitation from an irritable focus in the atria as in paroxysmal tachycardia If the path is shortened or its speed increased the atrial rate per minute increases and if this exceeds 400 per minute it becomes irregular When the excitatory process becomes very rapid and irregular it is no longer called atrial flutter but atrial fibrillation there is a wide boundary between the two clear cut conditions which may be termed flutter fibrillation Although atrial flutter and atrial fibrillation are closely allied in mechanism their separation is useful and important from the clinical standpoint

Atrial flutter has sometimes been regarded clinically as midway between atrial paroxysmal tachycardia and atrial fibrillation but it is much more closely related to the latter as evidenced for example by the electrocardiogram which in the case of atrial flutter shows constant movement of the baseline due to atrial activity (Figure 159) while in atrial paroxysmal tachycardia there are short atrial waves sharply differentiated and separated from each other (Figure 156 page 879)

Atrial flutter like fibrillation may be paroxysmal or permanent it is much more likely to be paroxysmal the paroxysms lasting usually for hours to days occasionally for weeks and rarely for months or years Paroxysmal atrial flutter occurs in three or four times as many cases as does permanent atrial flutter

Etiology *Cause* The precise way in which atrial flutter is started is not clear but predisposing conditions are for the most part known Like atrial

fibrillation atrial flutter is more commonly found in the presence of heart disease than in its absence It is especially likely to occur in mitral stenosis hypertension thyrotoxicosis and coronary heart disease but it exists sometimes alone with no evidence of heart disease or any other pathologic condition An otherwise perfectly healthy strong person may have atrial flutter Whether it is the only abnormality or one associated with serious disease it is commonly precipitated by sudden effort nervous excitement trauma or surgical operation particularly involving the thorax rarely it begins without apparent provocation

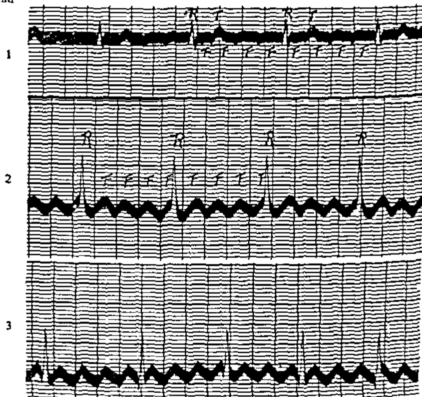


FIG 159 Electrocardiogram showing atrial flutter Three leads Four to one and three to one atrioventricular block

In a series of 52 cases of atrial flutter observed by Parkinson and Bedford (1927) between the years 1913 and 1926 there were the following etiologic findings chronic rheumatic heart disease in 14 cases (27 per cent) acute rheumatic infection in 2 cases other acute febrile illnesses in 3 thyrotoxicosis in 2 hypertension in 6 myocardial infarction in 3 a positive Wassermann reaction in 3 cardiac enlargement other than rheumatic hypertensive or syphilitic in 13 congenital heart disease in 1 and no evidence of heart disease in 5 Of the 14 cases of chronic rheumatic heart disease 7 showed mitral

stenosis alone 4 mitral stenosis and aortic regurgitation 2 mitral disease without clinical evidence of stenosis and 1 aortic regurgitation alone

Sex The sexes are represented unequally in statistics so far available the male sex preponderating in about the ratio of 3 to 1 The cause for this difference is not clear except that the male sex is generally under greater strain than the female sex

Age The incidence of atrial flutter is much greater in later decades of life than in youth three fourths of the cases occurring after the age of forty years However it is encountered in children and even in infants

Pathology *There are no known structural changes in the myocardium characteristic of atrial flutter* There may be extensive heart disease or there may be none the abnormal finding more often noted than any other in a heart with atrial flutter is mitral stenosis

Symptoms The typical symptom of atrial flutter is rapid regular forceful palpitation sometimes described by the patient himself as heart flutter but not distinguishable in sensation from paroxysmal tachycardia There may or may not be symptoms of congestive failure coincident with or in some cases induced by the atrial flutter congestive failure is likely to occur if the atrial flutter is of long duration in persons with damaged hearts Pain is rare precordial aching may occur The alarm occasioned by the atrial flutter may be so great that much nervous excitement and even a state of nervous prostration may exist If the ventricular rate is very rapid as sometimes happens when there is no block (1 1 rhythm) and the heart rate approaches 300 per minute weakness dizziness faintness or even actual syncope may occur associated with cerebral anemia and other effects of the very small output of blood and much reduced blood flow

Signs The characteristic sign of atrial flutter is the regular rapid heart rate which is maintained often with variations of but a few beats from minute to minute for days weeks or months at a time in spite of exercise rest and sometimes even drug therapy The apex rate and usually also the radial pulse rate average about 150 per minute while electrocardiograms show double this rate for the atrial action (about 300 per minute) in approximately half of the cases of atrial flutter when first seen Sometimes the heart rate is found to be irregular even before treatment due to varying grades of block usually 1 1 2 1 3 1 or 4 1 coming in regular or quite irregular sequences so that the arrhythmia may be an orderly one or a very disorderly one *Sometimes the* heart rate is regular and very fast (with 1 1 rhythm) or regular and slow (with 3 1 4 1 6 1 or even 8 1 block regularly maintained) These variations of block thus account for that half of the cases of atrial flutter without a constant 2 to 1 block Although great and irregular variation of grades of atrioventricular block may produce a heart action that seems on cardiac auscultation or on palpation of the pulse to be absolutely irregular careful study and especially measurement of the arteriogram will show the existence of a dominant rhythm whereby for example four pulse intervals of 2 to 1 block will equal in duration two pulse intervals of 4 to 1 block this finding of a definite

dominant rhythm rules out atrial fibrillation even without an electrocardiogram but the measurements are sometimes difficult and obscure Some cases that happen to have atrial flutter with an atrial rate of about 300 and 4 to 1 heart block which occurs either spontaneously or after treatment are almost sure to escape notice clinically because of their regular slow heart action and pulse rate of about 75 unless phlebograms or electrocardiograms are taken This infrequent but important happening is a further illustration of the value of graphic records (see Figure 159, page 914)

Related to the natural tendency for atrial flutter to show a v block is a clinical test for this disorder of rhythm It is the rule for firm pressure by the fingers over the carotid sinus on either side of the neck to increase the grade of block and so to slow the heart rate to one half or even less during the application of the pressure the fast and regular rate quickly returning on release of the pressure to its original high level Thus a ventricular rate of 150 with 2 to 1 block in atrial flutter can drop to 75 with the change to 4 to 1 block Such a change does not occur in sinus tachycardia while if a sharp drop of heart rate occurs in the case of atrial paroxysmal tachycardia when pressure is applied to the carotid sinus it means that the paroxysm has been abolished and so the rate does not go up again directly the carotid sinus pressure is released

In doubtful cases when atrial flutter is possible or suspected electrocardiograms should be obtained they are far superior to clinical signs or tests and to phlebograms because they not only reveal the atrial action more clearly but they distinguish at once between atrial flutter and atrial paroxysmal tachycardia and moreover they afford other information about the cardiac mechanism The flutter waves produced in the electrocardiogram by the atrial action are best shown by a special lead with exploring electrode over the third intercostal space just to the right of the sternum they are almost always well seen in Leads 2 and 3 but are often so poorly marked in Lead 1 and in the routine precordial leads over the right and left ventricles (V to V_6 inclusive) that the interpretation from these leads may remain in doubt

Roentgen ray study in atrial flutter is of relatively little value although in some cases the abnormal mechanism may be observed fluoroscopically

With atrial flutter there may or may not be signs of cardiac enlargement valvular disease pericarditis aortic disease hypertension or congestive failure in half the cases or more there are such signs

Special tests may show a decreased blood flow when the heart rate is very rapid but this will return to normal when the ventricular rate falls if there is no heart failure With very fast heart rates the systolic blood pressure also tends to be low (100 mm or less) and the pulse pressure small (20 to 30 mm)

Course and prognosis Clinically atrial flutter falls midway between atrial paroxysmal tachycardia and atrial fibrillation as regards significance and duration It is more important than paroxysmal tachycardia because it is found more often with heart disease and lasts longer but it is somewhat easier to

control It is somewhat less important than atrial fibrillation because it is less often permanent and is less likely to be associated with serious heart disease the heart rate is however harder to control Generally atrial flutter lasts for hours days or weeks rarely for minutes months or years We have observed an instance of atrial flutter lasting five years with ventricular rate for most of the time at 130 per minute (2 to 1 atrioventricular block) or 260 (1 1 rhythm) not responding to treatment but stopping spontaneously and leaving no trace of heart disease (Sprague and White 1928) Lewis has known atrial flutter to last uninterruptedly for twenty four years the ventricles beating without cessation at 140 per minute (Lewis 1937) and Kossman and Berger (1941) have reported an instance of eleven years duration we have had another case under our own observation for twenty six years who is still in good health with no other evidence of heart trouble than the presistent atrial flutter

The condition starts abruptly and usually either stops abruptly or changes suddenly or slowly to atrial fibrillation the ventricular rate usually falls through increase of the grade of heart block under digitalis therapy It often is a disagreeable and more or less crippling condition but it is rarely dangerous In a few cases generally with serious heart disease atrial flutter of long dura tion and not yielding to treatment leads to heart failure and may even cause death

Complications Congestive heart failure atrial thrombosis and embolism may occur as complications of atrial flutter but they are less common than in the case of atrial fibrillation

Treatment Atrial flutter is more amenable to digitalis therapy than to quini dine therapy and it is wiser to use digitalis than any other drug in the treat ment of established flutter If there is but a brief paroxysm lasting a few minutes or at most a few hours no treatment at all may be necessary other than rest and reassurance

When atrial flutter has lasted for more than a few hours digitalis therapy should be started preferably 0 2 gm (3 gr) of the standardized powdered leaf or digitoxin 0 2 to 0 3 mg by mouth three times a day for two or three days as needed In emergencies when the tachycardia associated with the flutter causes great distress or myocardial failure the digitalis can of course be given intravenously as described for atrial fibrillation earlier in this chapter (see page 905) If the atrial flutter persists after three days but the ventricular rate has been reduced to normal figures by increase in the grade of block (4 to 1 or more) the digitalis leaf may be reduced to a daily ration of 0 06 or 0 1 gm (1 or 1½ gr) or the digitoxin to 0 1 to 0 2 perhaps best 0 15 mg to maintain the full drug effect so long as is necessary If atrial fibrillation has been induced the digitalis may be continued to maintain a slow ventricular rate or it may be dropped to see whether or not normal rhythm will soon follow as it sometimes does this latter was once thought to be the usual (classical) course When normal rhythm does return the continuance of

treatment is not necessary except for the avoidance of factors which may induce a return of the atrial flutter and a prophylactic dose of quinidine sulfate 0 2 gm (3 gr) four times a day for a few days may be used

Quinidine sulfate may be administered in the way described for atrial fibrillation earlier in this chapter to cases not responding to digitalis or to cases believed amenable to quinidine for the purpose of restoring normal rhythm at the outset or after the atrial fibrillation into which it is converted has become fixed whether or not there is a slowing of the heart rate by digitalis

In about half the cases of atrial flutter digitalis therapy is successful in another few cases quinidine is successful when digitalis fails in others digitalis is partly successful in that a satisfactorily slow heart rate is produced although atrial flutter or fibrillation continues and in rare cases neither digitalis nor quinidine controls either the atrial mechanism or the ventricular rate the attack of flutter stopping spontaneously perhaps after months or even years The best course generally to pursue is first to digitalize the patient with atrial flutter and then if normal rhythm is not restored to try a course of quinidine sulfate

Complications of atrial flutter like congestive failure demand treatment as much as does the disturbance of heart rhythm digitalis is especially valuable in this respect for it is the best therapy for both the atrial flutter and the congestive failure If the situation is urgent the drug may be given intravenously as stated above

Finally to prevent paroxysms of atrial flutter or a recurrence of permanent flutter care should be taken to avoid exciting factors—fatigue physical or mental sudden exertion overeating excessive use of tobacco alcohol tea or coffee infections focal or general unnecessary surgical operations and congestive heart failure Rations of quinidine sulfate 0 2 gm (3 gr) three or four times a day or of digitalis 0 06 or 0 1 gm (1 or 1½ gr) daily after digitalization are also sometimes effective just as they are in reducing the number and duration of paroxysms of tachycardia or of atrial fibrillation such drugs should be used as needed but not necessarily as a routine in every case

Differential diagnosis Atrial flutter is to be differentiated from sinoatrial tachycardia paroxysmal tachycardia and atrial fibrillation Its long duration with rapid steady heart rate under various circumstances the absence of fever thyrotoxicosis and excitement which might be responsible for sinoatrial tachycardia and the frequent presence of heart disease help to distinguish atrial flutter from rapid normal rhythm The long duration of the paroxysms of atrial flutter the more common association with heart disease and the tendency of carotid sinus pressure to slow the heart rate temporarily by increasing the grade of block but not to abolish the abnormal rhythm distinguish flutter clinically from paroxysmal tachycardia The regularity of rhythm is the essential characteristic which ordinarily differentiates flutter from fibrillation It is often necessary however and always wise to obtain an electrocardiogram to be sure of the diagnosis of atrial flutter

VENTRICULAR FIBRILLATION AND FLUTTER

Ventricular fibrillation consists of an apparently incoordinated ventricular action with cessation of regular contraction resulting in death if effective ventricular action is not speedily resumed It was first noted in 1850 by Hoffa and Ludwig in the laboratory As a temporary or terminal condition it is frequently seen in experimental animals as in the dog and cat and it has occasionally been encountered in human electrocardiograms in dying patients It probably is commonly a terminal condition in man but an actual cause of death only under certain circumstances as in fatalities resulting from the blocking of the coronary circulation and in death during chloroform anesthesia from acute benzol poisoning and from electrocution which procedures have been shown to cause ventricular fibrillation in experimental animals and in rare instances in man The smaller the heart in experimental animals the greater the chance for restoration of normal rhythm the human heart may be too large to permit frequent recovery even if ventricular fibrillation were of frequent occurrence

A number of human electrocardiograms showing ventricular fibrillation have been published but the separation electrocardiographically between ventricular fibrillation and ventricular paroxysmal tachycardia and flutter is not a sharp one and the interpretation is sometimes in doubt A clear-cut instance is shown in Figure 160

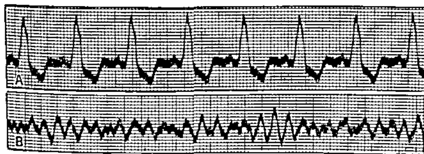


FIG 160 Electrocardiograms of a case with bundle branch block (*A*) who died in an attack of ventricular fibrillation (*B*) (Graybiel and White *Electrocardiography in Practice* 1941 Kindness of W B Saunders Company Philadelphia)

The mechanism of ventricular fibrillation is obscure it may be similar for the ventricles to that of atrial fibrillation for the atria it may consist of an irregular circus movement or there may be multiple spread or foci of ventricular activity

The relationship of the mechanisms of ventricular paroxysmal tachycardia and ventricular fibrillation seems close the former tending to evolve into the latter via an intermediate mechanism *ventricular flutter* which has been discussed recently by Fastier and Smirk (1948) and which is very rapid but

regular One of the most authoritative opinions concerning the pathologic physiology or mechanism of ventricular fibrillation is that presented by Wiggers in 1940 After stating that the process is an evolution of changes from the moment of its inception until it ceases completely in the course of 30 to 45 minutes Wiggers writes that the available evidence favors the conclusion that after a single premature systole the phenomenon is caused by re-entry of circulating wave fronts which involve smaller and smaller blocks of myocardium each of which develops an independent excitation As a result of the anoxia which develops progressively after the cessation of coronary flow conduction is slowed and the vigor of fractionate contractions decreased The resultant of these changes causes in succession the undulatory convulsive tremulous and atonic stages of its evolution Wiggers has been able to carry out defibrillation experimentally in dogs by passing strong alternating currents for brief intervals of 0 1 to 5 seconds through the ventricles provided such countershock is applied within approximately two minutes Application of comparable electric shock by chest electrodes to man would Wiggers states be dangerous to both operator and patient Massage of the heart in the case of dogs with more prolonged asystole has aided in the recovery of the heart by the countershocks

Clinically ventricular fibrillation and flutter are conditions of uncertain importance in the present state of our knowledge They have been encountered after massive doses of digitalis and after epinephrine (adrenaline) as an end stage of ventricular paroxysmal tachycardia and in a few patients dying with other conditions They are probably commonly a terminal event after coronary thrombosis and during chloroform anesthesia and electrocution They are also a hazard in cyclopropane anesthesia They have been noted in rare cases dying of angina pectoris while being electrocardiographed and have been found in individuals dying of some infectious diseases However they are not the only mechanism of heart death depression of the pacemakers and of atrioventricular conduction being found more often Syncope transient or leading to death and simulating the Adams Stokes syndrome has been reported in several cases of prolonged ventricular fibrillation it is always very ominous Recovery has been rare

It is probable that quinidine sulfate does help to prevent fibrillation of the ventricles if given in moderate dosage to individuals threatened with this usually fatal arrhythmia especially in cases of recent myocardial infarction or those subject to paroxysms of ventricular tachycardia but as yet we have no certainty of this Borg (1939) suggested its use in all cases of coronary insufficiency and believes that he reduced the mortality in coronary heart disease thereby My own experience makes me think that he is right but adequate statistical proof is still lacking Acetylcholin (acetyl B methylcholin chloride) and papaverine have been shown in experimental animals to act prophylactically (Nahum and Hoff 1934 and Lindner and Katz 1941 respectively)

In the last edition of this book it was stated that there was no specific

therapy once ventricular fibrillation has begun However Beck et al (1941 and 1947) have demonstrated that if the heart is exposed an electric shock of 110 volts and 1 15 amperes can restore the normal heartbeat They have reported success in one case of ventricular fibrillation of long duration

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CHAPTER 34

BRADYCARDIA AND HEART BLOCK (SINOATRIAL, ATRIOVENTRICULAR, AND INTRAVENTRICULAR) VENTRICULAR ESCAPE ATRIOVENTRICULAR NODAL RHYTHM SUDDEN DEATH

Heart block in its various manifestations the subject of the present chapter is primarily the result of depression of the specialized tissues that normally initiate the heartbeat (sinoatrial and atrioventricular nodes) and conduct it to the muscle of both ventricles (atrioventricular bundle and its branches) in contrast to the abnormal cardiac rhythms due to unusual excitability and stimulation that have been considered in the last two chapters When the sinoatrial node is much depressed we have *sinoatrial block* often with control of the heartbeat by the atrioventricular node if this lower nodal pacemaker initiates occasional beats we speak of *ventricular escape* if it controls the ventricular rhythm entirely we speak of an *idioventricular rhythm* and when it controls atrial as well as ventricular action with sinoatrial node wholly silent we speak of *atrioventricular nodal rhythm* Delay or more or less complete blocking of the impulse (initiated by the sinoatrial node) in the atrioventricular node and bundle gives rise to *atrioventricular block* while delay or blocking of the impulse in the bundle branches causes *intraventricular block* or *bundle branch block* The immediate causes (mechanisms) of sudden death are (1) complete depression of both nodes (2) a complete blocking of the atrial impulse above the ventricular muscle with paralysis of the lower nodal and bundle pacemaker and (3) ventricular fibrillation (see Chapter 33 for this last named disorder)

SINOATRIAL BRADYCARDIA SINUS ARRHYTHMIA AND BLOCK. ATRIAL STANDSTILL VENTRICULAR ESCAPE

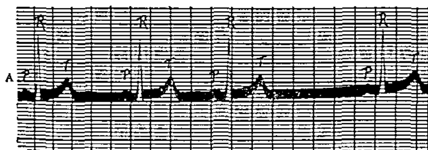
Mechanism If the normal pacemaker the sinoatrial node is depressed the heart rate slows *sinoatrial bradycardia* is the term applied to this slowing of

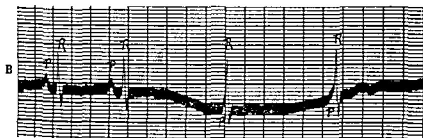
the whole heart Often associated with the bradycardia is *sinus arrhythmia* (Figure 161A) If it happens that occasionally or frequently there appears between atrial beats an interval which is equal or almost equal to two usual cycles the condition is called *partial sinoatrial block* if the atrial rate becomes very slow (35 or less per minute) whether regular (as it usually is) or irregular the condition is sometimes termed high grade sinoatrial block and if the atrial contractions drop out altogether the ventricles continuing to beat as the result of independent stimulation from the atrioventricular node a condition results which has been called *complete sinoatrial block atrial standstill* or *atrial paralysis*

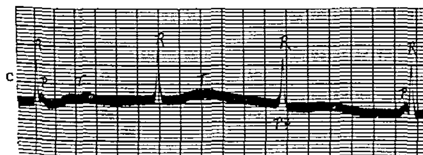
Incidence *Sinoatrial bradycardia* is normal and unimportant except when of extreme degree that is when the whole heart rate sinks below 35 or less per minute A sinoatrial rate of 50 or 60 is common in many normal individuals at rest sometimes during sleep or on first waking in the mornin the heart rate may be as slow as 45 Sinoatrial bradycardia can frequently be produced by *vagal stimulation* most readily by pressure over the right *carotid sinus* in normal persons or in patients whose heart rate is already rather slow and especially if digitalis has been previously given in moderate or large dosage Occasionally in a normal person carotid sinus pressure may slow the heart excessively and faintness and even syncope have been caused by such tests especially if the carotid sinus is sensitive If the pulse is fast usually because of sympathetic nerve stimulation carotid sinus pressure is much less effective except in a few cases when it may abolish paroxysmal tachycardia or increase the grade of heart block already present in atrial flutter Pressure on the left side of the neck and on the eyeballs (oculocardiac reflex) may also slow the heart by causing depression of the sinoatrial pacemaker through vagal stimulation but pressure in such places is usually less effective than right carotid sinus pressure Voluntary slowing unlike voluntary acceleration of the heart rate is not directly possible, the individuals who have been reported to have slowed their pulse voluntarily have apparently caused bradycardia reflexly by respiratory effort or have obliterated their radial pulse by muscular movements of the thorax mainly by an upward and backward shrugging of the shoulders thereby compressing the subclavian arteries Athletes sometimes show an abrupt fall in heart rate even a halving shortly after the completion of some special effort this apparently is a normal vagal reaction which tends to be much accentuated by training

It is very important to remember that a heart rate in the forties or even in the thirties per minute at rest can be a perfectly normal occurrence especially in athletes in training and particularly in distance runners (White 1942)

Etiology *Cause* Pathologic degrees of sinoatrial bradycardia block and arrhythmia are seen rarely They are most commonly produced by digitalis in excessive dosage and in individuals whose tolerance for the drug is low Other drugs of the digitalis group and quinidine sulfate (and allied cinchona alkaloids) can also depress the sinoatrial node in high degree Vagal irritation by excessively sensitive carotid sinus by direct pressure of tumors by infec







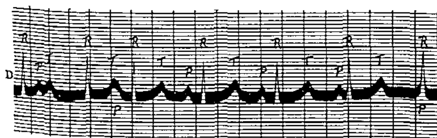


FIG 161 Electrocardiograms (Lead 2) showing (*A*) sinus arrhythmia and brady cardia or block (*B*) sinus arrhythmia with ventricular escape induced by deep breathing (*C*) atrioventricular dissociation due to independent action of sinoatrial and atrioven tricular pacemakers at almost the same rate (50 per minute) and (*D*) atrioventricular dissociation due to escape of the atrioventricular nodal pacemaker at a rate of 90 per minute

tion in the neck or mediastinum and by intracranial tumors and high intra cranial tension has likewise been reported as a cause of sinoatrial block Sometimes the heart abruptly ceases to contract during anesthesia or surgical operations Heart disease itself is a very rare cause of sinoatrial block but obstruction of blood supply to the sinoatrial node by atheroma or occlusion of its artery has been thought responsible in a few cases Lesser degrees of bradycardia with rates of 45 to 55 are occasionally found in certain diseases such as epidemic parotitis and jaundice of either infectious or obstructive origin and sometimes during convalescence from any acute illness such as influenza

The commonest of these conditions is simple sinoatrial slowing with regular heart action at rates of 30 to 40 less often there is gross sinus arrhythmia at these rates the dropped beat is rare and least common of all is complete atrial standstill

Both *sexes* and all *ages* are subject to these disorders of the sinoatrial mechanism but they are more common in youth It was once thought that well marked sinus arrhythmia was a sign of a healthy heart this is not so but it is true that in the absence of some special cause like a digitalis effect it is found more often in youth than in old age and it is abolished by the sympathetic stimulation that comes with infection for example rheumatic infection To this extent then sinus arrhythmia is a sign of a healthy heart in that heart disease is less common in youth than in old age and less common in young persons without active infection than in those with such infection especially in a rheumatic environment There is one exception to these remarks for infrequently in elderly persons with arteriosclerosis or heart disease a con siderable degree of sinus arrhythmia may be found as a distinctly abnormal sign (Faulkner 1930)

Symptoms There are no particular symptoms of sinoatrial bradycardia If the rate is very slow or irregular there may be disagreeable palpitation or even weakness dizziness and syncope when the periods of standstill are prolonged In fact the marked slowing of the pulse with syncope and con vulsions that may rarely result from extreme sinoatrial nodal depression is indistinguishable from the Morgagni Adams Stokes syndrome found with atrioventricular block unless graphic records are taken Symptoms of con gestive failure are rare Nervous symptoms are common for the subjects of sinoatrial nodal depression may also have neurocirculatory asthenia

Signs The one sign of sinoatrial depression is the slow heart rate originating in the atria (Figure 161A page 927) There may or may not be arrhythmia but it is rarely absolute so that there is little likelihood of confusion between atrial fibrillation with atrioventricular block and sinoatrial depression When there is doubt an exercise test will make the pulse more regular in the case of sinoatrial arrhythmia and bradycardia with increase in rate while the pulse in atrial fibrillation will become more irregular There may or may not be signs of heart disease heart failure or hypertension Roentgen ray study is of little or no value Electrocardiography affords the greatest aid for it usually reveals

at a glance the abnormal mechanism and the relationship of atrial and ventricular activities (Figure 161)

At times in sinoatrial bradycardia the electrocardiogram shows that there is not always a normal atrioventricular sequence The atrial rate may be so slow that the idioventricular pacemaker in the atrioventricular node does not wait for the impulse from the sinoatrial node but escapes Such *ventricular escape* may be for one beat only or it may be for a group of beats (Figures 161B C and D page 927) or if the atria are wholly paralyzed it may constitute the entire cardiac mechanism (Figure 162) Ventricular escape is of no particular clinical significance but it constitutes an interesting physiologic adjustment of the body in case of need It sometimes has been confused with heart block and so labeled wrongly it is to be sure atrioventricular dissociation but it is not atrioventricular block It has sometimes been called *interference dissociation* when both nodes are active without true heart block (Figure 161D)

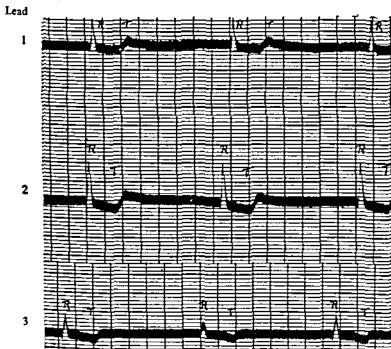


FIG 162 Electrocardiogram showing atrial standstill No evidence of *P* waves in any of the three leads Digitalis inversion of *S T* segments and *T* waves A jugular phlebogram also failed to show any evidence of atrial activity in this case

The **course, complications, and prognosis** of disturbances of sinoatrial rhythm due to depression are generally of little clinical importance As a rule the condition is a transient anomaly perhaps surprising and sometimes disagreeable but only rarely dangerous In extreme cases there may be syncope and even death due probably to paralysis of the ventricular pacemaker also

as with poisoning by quinidine or digitalis and with sudden standstill of the heart during anesthesia and surgical operations

The **treatment** consists of the omission of the toxic agent for example digitalis or quinidine or of the control of other underlying cause such as cerebral disease For marked bradycardia with faintness or syncope drugs may be needed atropine sulfate 1 mg (1/60 gr) or more subcutaneously every four hours as needed if vagal stimulation is the chief factor, otherwise epinephrine (adrenaline) or ephedrine Epinephrine hydrochloride may be given subcutaneously intravenously or even into or over the heart directly to stimulate a resumption of normal beating Life has apparently been saved in a number of cases by the intracardiac injection of 0 5 cc or less of a 1 1 000 solution of epinephrine hydrochloride after the heart has stopped beating during anesthesia and surgical operations or obstetric procedures or in smaller dosage (0 1 cc) in stillborn infants This is an emergency treatment which should always be borne in mind and although it may often prove fruitless an occasional rescue makes it of decided value Cardiac massage when possible is however much more effective and wiser than the use of drugs and steps should more often be taken to carry it out to save lives otherwise doomed artificial respiration should be carried on simultaneously If serious heart disease is back of the cardiac standstill resuscitation by any method is very unlikely to succeed cardiac massage and electric shocks plus artificial respiration may conceivably be successful even in such cases but the difficulties of carrying out this therapy are almost always insurmountable

Ephedrine hydrochloride may be given in the dosage of ¼ to ½ gr (15 to 30 mg) by mouth three or four times a day instead of epinephrine as prophylaxis against cardiac standstill but it is much less likely to be effective the same statement applies in general though to a lesser degree to the more recently introduced Paredrine given in the dosage of 40 to 60 mg by mouth three times daily (Nathanson et al 1942)

If an excessive sensitiveness of the carotid sinus on either side is found as a basis for syncopal attacks a cure can be effected by carotid denervation but it is very important first to rule out atrioventricular block revealed or increased by the effect of a normal carotid sinus reflex

For lesser grades of sinoatrial bradycardia block and arrhythmia no treatment at all is necessary The importance of the condition is often overemphasized and reassurance is more needed than anything else with discontinuance of various unnecessary remedies At times the most useful of all measures is electrocardiography to establish the diagnosis of an unimportant sinus arrhythmia or bradycardia and to rule out atrioventricular block which perhaps had been suspected as an aftermath of some serious infection such as influenza or pneumonia Almost invariably the supposed heart block present during convalescence from some important infectious disease proves to be merely sinoatrial bradycardia

Intra atrial block that is defective conduction of the wave of excitation and contraction through the atrial muscle itself has been produced and studied

in experimental animals it may be caused by certain poisons, such as quinidine sulfate and digitalis and by vagal stimulation When of high degree the excitation wave may be so diverted as to alter the shape of the *P* wave of the electrocardiogram Its existence in man has been indicated by variations in shape and rhythm of the atrial waves of the electrocardiogram for example during quinidine therapy but its clinical importance has not been established except in atrial flutter and atrial fibrillation

Interatrial block partial and complete has been produced and studied in experimental animals but its occurrence in man although suggested and described has not been conclusively proved To effect independent action of the two atria very extensive structural or functional changes would be necessary to block off all the extensive muscle tracts joining the two atria

ATRIOVENTRICULAR NODAL RHYTHM

A rare but interesting abnormal heart rhythm in man is that which originates in the atrioventricular node in the junctional tissues and controls both atrial and ventricular contractions Atrioventricular nodal rhythm differs from ventricular escape and idioventricular rhythm only in that the atria as well as the ventricles are controlled by this lower pacemaker the sinoatrial node or other atrial pacemaker being superseded at least for the time being The obstinacy of the atrium in maintaining its own pacemaker accounts for the great rarity of atrioventricular nodal rhythm Occasionally unusual irritation or irritability of the junctional tissues accounts for premature beats or paroxysmal tachycardia of atrioventricular nodal origin but a steady rhythm at a slow rate arising from the junctional tissues is another matter and it is this that is called atrioventricular nodal rhythm (Figure 163 page 932)

Three conditions are necessary for the establishment even for a short time of atrioventricular nodal rhythm (1) marked depression of the normal pacemaker of the heart situated in the sinoatrial node and failure of any other part of the atrial muscle to assume its role (2) normal activity (potential or latent ordinarily) of the pacemaking function of the atrioventricular node and (3) ability of the impulse to pass backward from the junctional tissue into the atria to cause their contraction that is an absence of a state of reversed block The rate of impulse formation in the atrioventricular node averages in man about 40 per minute with a range of 30 to 50 and that heart rate therefore is usual in atrioventricular nodal rhythm The heart action is as a rule quite regular sometimes absolutely so but at times there is more or less irregularity as in the case of sinus arrhythmia due to vagus and sympathetic nerve action on the junctional tissues It is at times possible by vagal stimulation or through the action of digitalis to depress the reversed conduction to the atria and so to delay the ventriculoatrial interval and even block off the atrial response altogether that there may be atrial standstill with persistence of ventricular action (idioventricular rhythm) (Figure 162 page 929) Release of vagal inhibition by atropine or sympathetic stimulation by exercise

may first shorten the ventriculoatrial conduction time and then restore sinoatrial nodal function and normal heart rhythm

Atrioventricular nodal rhythm is a rare clinical condition it is unimportant except that it should be differentiated from the more serious disturbance of heart block It can be studied satisfactorily only by electrocardiogram although a phlebogram from the jugular pulse may indicate its presence Inspection of the jugular pulse (without a tracing) and fluoroscopic observation of the superior vena cava may show a very prominent pulsation due to coincidence of atrial and ventricular contractions suggesting this unusual rhythm but confirmation by electrocardiogram is necessary Any uniformly regular pulse at a rate of 35 to 40 per minute should be investigated to learn whether it is due to atrioventricular block (most likely) to sinus bradycardia (less

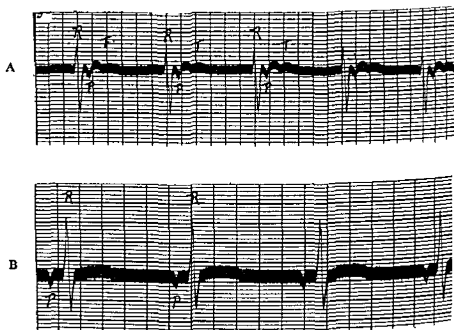


FIG 163 Electrocardiograms (Lead 2) showing atrioventricular nodal rhythm Two types (*A*) with *P* wave following the *QRS* wave and (*B*) with the *P* wave preceding the *QRS* wave

likely) or to atrioventricular rhythm (rare) As a rule in atrioventricular nodal rhythm the atrial contraction follows the ventricular contraction less often it coincides exactly with it and very infrequently precedes it (Figure 162) The *P* wave in the electrocardiogram is usually inverted and found at an interval of 0 1 to 0 2 second after the onset of the *QRS* wave it has been described as upright in rare cases due to an unusual position of the atria or unusual course of the excitation wave in the atria in relation to the axis of Lead 2 of the electrocardiogram If the atrial contraction follows the ventricular by a considerable interval usually over 0 2 second a second ventricular

contraction may in turn follow the atrial contraction producing a bigeminal heart action with one atrial contraction between two ventricular beats This is a rare phenomenon that has been noted in a few cases

Unusual sinoatrial nodal depression from the effect of digitalis or other cause generally unknown has been responsible for the occasional cases of atrioventricular nodal rhythm seen clinically The diagnosis usually an unexpected one has been made by electrocardiogram The condition is generally temporary or recurrent lasting for a few beats minutes or hours at a time and alternating with normal rhythm rarely it lasts for weeks or months or as a recurring condition for years There may or may not be heart disease associated with it usually there is not The prognosis is dependent on other findings and not on the atrioventricular nodal rhythm which appears to be a harmless condition not needing treatment in itself and not easily controlled by any special therapy

ATRIOVENTRICULAR BLOCK

Depression of the function of conduction of the atrioventricular node (of Tawara) and bundle (of His) which join atrial and ventricular muscle results in delay or obstruction of the excitation wave as it travels downward from the atria to stimulate the ventricles This delay in conduction has been called atrioventricular block in early days it was known simply as *heart block* for it was the first kind of block to be recognized being described long before the special tissue itself was discovered

Incidence Atrioventricular block is undoubtedly more common than statistics show for slight grades are easily and probably usually missed inasmuch as electrocardiograms are taken of relatively few patients The higher grades of atrioventricular block are however certainly far less common than are premature beats atrial paroxysmal tachycardia and atrial fibrillation they are more common than atrial flutter and ventricular proxysmal tachycardia In the fifteen years from 1916 to 1930 inclusive at the Massachusetts General Hospital in an electrocardiographic series of 10 000 patients with cardiac symptoms or signs atrioventricular block was diagnosed in 641 cases (6 4 per cent) The block was complete in 79 or 12 per cent of these 641 cases and partial in 562 or 88 per cent (296 of the 562 cases of partial block showed only a delayed *P R* interval) In another series of 69 cases of atrioventricular block coronary disease was apparently responsible in 35 (50 7 per cent) rheumatic infection in 19 (27 5 per cent) congenital defect in 1 syphilitic involvement in 1 digitalis medication in 9 and an unknown factor (probably congenital) in 4 cases (White and Jones 1928) In another series of 74 cases a congenital etiology was diagnosed in 14 per cent rheumatic heart disease in 4 per cent syphilis in 7 per cent and other myocardial disease probably coronary in type in 75 per cent (Campbell 1944)

Mechanism (abnormal physiology) Atrioventricular block or defective atrioventricular conduction is due to the failure of the atrioventricular node

and bundle to transmit the excitation wave at a normal rate from atria to ventricles because of destruction from disease or because of prolongation of the refractory period resulting from disease faulty nutrition vagus nerve action or fatigue from excessive speed of stimulation as in extreme tachycardia Atrioventricular block is a more or less normal phenomenon in atrial fibrillation atrial flutter and very rapid atrial paroxysmal tachycardia when the atrial rate is so fast over 200 and often over 300 per minute that even perfectly normal atrioventricular junctional tissue cannot resume a responsive state between successive stimuli in such cases 2 to 1 or higher grades of block quite naturally are found In these patients such block is of no serious significance in fact it is actually helpful for the heart and circulation Treatment of atrial fibrillation and atrial flutter consists chiefly of attempts to increase the grade of block in order to reduce the ventricular rate

When however at normal or only moderately accelerated speed of atrial activity there is delay or obstruction to the passage of the impulse to the ventricles an important type of atrioventricular block exists Although the block may originate in any part of the short tract of junctional tissue between the atrial muscle and the bifurcation of the bundle into its two branches which pass to right and left ventricles respectively and even in these branches themselves if both are affected the most susceptible and probably one of the commonest sites of blocking is at the very point where atrial muscle enters the junctional tract this has been shown by animal experiments and clinical observations (Lewis White and Meakins 1914 White 1915) It appears likely that toxic and nervous influences act chiefly at this point although destructive lesions are more common lower down that is in the bundle itself

Atrioventricular block may be temporary and functional or permanent and organic It may be of all grades from very slight delay in conduction so that the P R interval of the electrocardiogram measures 0 21 second to complete block when no impulses at all pass through from atria to ventricles Any defect in atrioventricular conduction short of complete dissociation is called partial heart block By far the commonest of all grades of block are the lesser ones with simple delay in conduction without dropped beats (Figure 164) cases with such slight block usually pass unrecognized unless graphic records are taken The P R interval in these cases varies from 0 21 up to 0 50 second or even longer but intervals of over 0 30 second are decidedly rare Faulkner has reported a case in which the P R intervals actually exceeded the R R intervals in duration (Faulkner 1935)

Occasional dropped beats and higher grades of partial block in which every fourth atrial impulse is blocked (called 4 to 3 block because there are four atrial contractions to three ventricular contractions), or every third impulse is blocked (3 to 2 block) or every second (2 to 1) or every second and third (3 to 1) are usually easily recognized clinically and can often be analyzed simply by careful auscultation of the heart and by inspection of the jugular pulse though more easily by electrocardiogram (Figure 164)

Grades of partial heart block higher than 2 to 1 are very rare although

3 to 1 (Figure 164C) 4 to 1 and even 5 and 6 to 1 do occur As a rule the pacemaker in the atrioventricular node escapes and establishes an independent ventricular or idioventricular rhythm if the grade of block becomes greater than 2 to 1 Such a rhythm called complete heart block usually becomes established at ventricular rates of 35 or below most commonly at about 30

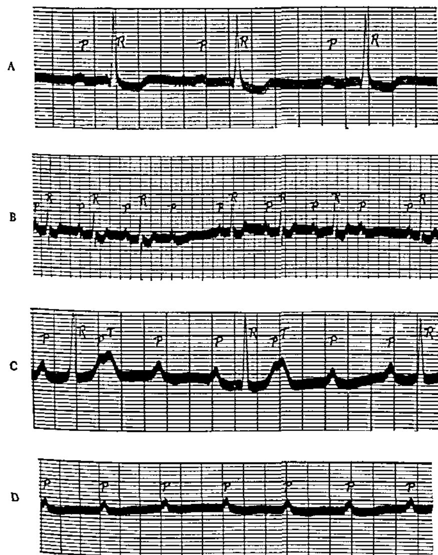


FIG 164 Electrocardiograms (Lead 2) of partial atrioventricular block (*A*) simple delay in conduction (*P R* interval = 0 32 second) (*B*) occasional dropped beats with varying *P R* intervals giving rise to the Wenckebach periods at the time of the dropped beats (unequal to the interval covering two usual beats) (*C*) three to one block and (*D*) entire absence of ventricular contractions during a Morgagni Adams Stokes attack Time interval = 0 2 second

per minute but higher in infants and young children for example at about 50 per minute Two to one atrioventricular block with an atrial rate at the normal average of 72 gives a ventricular rate of 36 which is but slightly higher than the usual rate in complete heart block These observations are important for they help to explain the occasional transitions back and forth between partial heart block and so called complete heart block which transitions have been sometimes regarded as mysterious Also they explain the rarity of long ventricular standstill and of the Morgagni Adams Stokes syndrome The atrioventricular nodal pacemaker usually escapes to prevent this syndrome rarely is it unable to do so because it is itself depressed Finally the observations noted above explain the occasional instances in supposedly complete heart block when an atrial impulse passes through the junction to give rise to a ventricular contraction In other words complete heart block does not mean that impulses can never pass from atria to ventricles

Rarely a state of double atrioventricular block exists in which there is not only complete dissociation between atria and ventricles but the idioventricular pacemaker itself may be blocked as in an early patient of my own whose electrocardiogram showed complete atrioventricular block and partial (2 to 1) idioventricular block (White 1918) and in a recent case of Langendorf and Katz (1942)

The ventricular rhythm in heart block of atrioventricular type may be regular or irregular Usually it is regular, due to the fact that there is simply a uniform delay in conduction time without dropped beats a regular 2 to 1 3 to 1 or complete block sequence also produces regular ventricular action but at slow rates of 40 to 20 When the ventricular action is irregular it is regularly irregular, for a dominant rhythm is maintained and in the arterial pulse equal spacing of large groups of beats against each other is possibl but equal spacing may not be found if comparison of the arrhythmia with the regular beats is limited to the pause due to the dropping of a beat since the interval between the beats preceding and following a dropped beat may or may not be equal to the length of two normal cycles it frequently is shorter because of the progressive delay that may occur in conduction (increasing *P R* intervals) up to the time of the dropped beat with marked shortening of the *P R* interval of the first beat after the pause due to recovery of the conducting tissue (Figure 164B page 935) This variation in conduction not only causes the pause in the arteriogram to be considerably shorter than the interval covered by two other cycles but it also results in some inequality in length of the normal' cycles (the pauses in heart block with dropped beats have sometimes been called Wenckebach s periods)

The atrial rate in a v block is usually regular but there may be any kind of atrial arrhythmia with any grade of block An interesting form of atrial arrhythmia is occasionally found in complete heart block and consists of a temporary quickening of the s a rhythm or prematurity of normal atrial complexes in the electrocardiogram when they fall directly after the ventricular contractions quite possibly due to the stimulus to the s a node by the

vigorous ventricular contraction Sometimes also even in complete a v block retrograde atrial contractions occur Atrial fibrillation is a not very rare accompaniment of complete heart block and atrial flutter has also been noted

Etiology *Cause* Atrioventricular block is caused either by temporary toxic or functional conditions by permanent organic disease or by both factors acting together It is most commonly temporary and functional but this type is likely to be missed because it is so transient and usually so slight in degree Examples of temporary or functional causes of atrioventricular block are asphyxia excessive vagal stimulation digitalis poisoning quinidine poisoning the effect of other vegetable or mineral poisons uremia and the temporary effects of certain infectious diseases such as rheumatic fever and diphtheria from which recovery may take place without persistence of heart block

Permanent and organic block is the result most frequently of extensive coronary disease There may be at first simply a narrowing of the vessel or vessels supplying the junctional tissues with blood with temporary or slight atrioventricular block which varies with the activity of the subject and with the state of the circulation With greater narrowing of the coronary vessels and limitation of blood supply the block becomes more permanent and greater in degree although the junctional tissue itself may show astonishingly little pathologic change Finally with great or complete arterial occlusion and obstruction to the blood supply the block may become complete and there may or may not prove to be extensive or complete degeneration and fibrosis of the atrioventricular bundle and node (actually a small infarct) An interesting occasional cause of paroxysmal a v block lasting for a few hours or a few days accompanying infarction of the posterior wall of the left ventricle is acute occlusion by thrombosis of the right coronary artery or of the circumflex branch of the left whence is derived the major part of the blood supply to the a v junctional tissues in almost all individuals Other less commonly acquired but important causes of permanent and organic block are virus diseases like epidemic parotitis (mumps) which have been more often recognized as factors in recent years syphilis acting directly by infection of the bundle of His or more often by pressure from adjacent gummata destructive lesions following diphtheria in rare cases the results of rheumatic inflammation invasion of the junctional tissue by the vegetative lesions of bacterial endocarditis and very rare causes like pressure from neoplasms and cysts miliary tuberculosis and trauma Finally atrioventricular block may be of congenital origin in rare cases associated with interventricular septal defects and abnormal course or development of the junctional tissues congenital block may be partial or complete

Sex The male sex shows permanent heart block twice as often as does the female probably because of the higher incidence of serious coronary disease in males but both sexes are about equally affected by temporary or functional block

Age Atrioventricular block is much more common in older persons because of their greater incidence of serious coronary disease About 90 per cent of

the higher grades of permanent heart block occur after the age of fifty years

Pathology No lesion at all may be found in the junctional tissues when there is transient or functional atrioventricular block rarely there may be no obvious lesion even with more or less permanent block of high grade On the other hand there may be considerable inflammation degeneration or fibrosis of the atrioventricular bundle and node without heart block Thus there is by no means a close correlation between the degree of atrioventricular block and the condition of the atrioventricular junctional tissues partly because of the fact that heart block is essentially a functional disturbance not necessarily dependent on obvious disease partly because the damage may be more in the coronary vessel or vessels supplying the node and bundle than in the node and bundle themselves and these vessels are not always carefully studied and partly because a small amount of tissue may be able to carry on normal function in spite of much damage or destruction of the bundle as a whole It is true however that permanent atrioventricular block of high degree is usually associated with extensive pathologic changes in the junctional tissue (inflammation degeneration or fibrosis) It is important in the postmortem study of the heart of a patient with atrioventricular block to examine the coronary vessels supplying the junctional tissues for narrowing or occlusion as well as to study the conducting tissues itself

Fibrosis of the bundle of His from coronary arteriosclerosis is the lesion most commonly found in heart block infiltration by rheumatic syphilitic or other infectious process like bacterial endocarditis and calcareous extension from the region of mitral or aortic valve which is calcified at its base is occasionally encountered while congenital defects of the bundle are rare As time passes we have become aware that now and then infectious diseases of childhood and youth may result in scarring of the junctional tissue which, quite symptomless may be wrongly ascribed to congenital or coronary etiology

It is of more than passing interest that atrioventricular block is an uncommon complication of massive coronary thrombosis with myocardial infarction diagnosable clinically while relatively few cases of atrioventricular block have had a history of acute clinical myocardial infarction The answer lies in the fact that occlusion of some of the larger coronary vessels may occur with serious heart damage but escape of the particular part of the heart in which lie the node of Tawara and bundle of His while a localized occlusion of the small vessels supplying these specialized structures creates too slight a clinical disturbance to be recognized in most cases the seriousness of the two conditions as evidence of important coronary heart disease is however much the same Of a series of 328 cases of clinical myocardial infarction analyzed only 3 6 per cent had atrioventricular block while of 117 patients with atrioventricular block only 11 9 per cent had had a history of myocardial infarction the frequency of angina pectoris was even less there having been but 1 5 per cent of cases of atrioventricular block among 700 patients with angina pectoris without clinical myocardial infarction and 9 4 per cent of cases of

angina pectoris without myocardial infarction among the 117 patients with atrioventricular block (Salcedo and White 1935)

Symptoms Atrioventricular block rarely causes any symptoms since it is usually of slight degree even block of high degree with dropped beats or very slow pulse may remain unnoticed by the patient Sometimes however there is complaint of a disagreeable palpitation due either to the pause in the heart s action when the atrial impulse is blocked to the forceful thump following the pause or to the constant pounding when the heart beats very slowly (about 30 per minute) The sensitiveness of the patient rather than the irregularity or slowness of the pulse determines the presence or absence of symptoms Pain and dyspnea are not common they are the result of complicating angina pectoris congestive heart failure or neurocirculatory asthenia

Much has been written in the past about the *Morgagni Adams Stokes* syndrome perhaps too much in view of its rarity Nevertheless it is an important complication of atrioventricular block when it does appear This syndrome as originally described consists in the association of syncope and epileptiform convulsions with marked slowing of the heart s action (Morgagni 1760 Adams 1827 Stokes 1846) but all grades of disturbance of the cerebral circulation may exist from slight dizziness and faintness with transient ventricular standstill of two or three seconds duration up to extreme degrees of the syndrome with cessation of the heartbeat for as long as twenty or thirty seconds (Figure 164D page 935) The patient with these distressing symptoms may have warning and find time to sit or to lie down or he may fall to the ground suddenly while standing or walking The clinical condition is similar to the result of the cerebral anemia occurring in some cases of extreme tachycardia or of atrial depression with standstill of atria as well as ventricles but the mechanism is of course quite different and the prognosis and treatment not the same It is better not to lump all these conditions into this one heading as has been somewhat the custom An electrocardiogram should be secured between attacks to see whether or not some degree of atrioventricular block is present As a rule sudden ventricular standstill due to atrioventricular block does not happen without at least some delay in conduction at other times rarely paroxysmal atrioventricular block does occur but graphic records are necessary for its proof

Signs The pathognomonic sign of atrioventricular block is either (1) delay in the interval between the atrial and the ventricular pressure waves in the venous pulse (*a-c* interval) beyond the normal usually put at 0 2 second or between the atrial and the ventricular electric waves in the electrocardiogram (*P R* interval) beyond the normal the upper limit of which is routinely placed at 0 2 second and with or without dropped beats (rare to many) (Figure 164 page 935) or (2) complete dissociation between atrial and ventricular rhythms with slow ventricular rate

A *P R* interval of 0 2 second is traditionally the upper limit of normal but such a measurement must be analyzed with care in every case The range of normal is wide in this particular as in many others (see Chapter 2) In infants

the normal varies from 0 08 to 0 14 second in children from 0 10 to 0 18 second and in adults from 0 12 to 0 22 second Thus 0 20 second would be well within the normal for one adult and prolonged for another whose average should be perhaps 0 15 second One must use considerable judgment and sometimes secure serial records over long intervals of time for sure appraisal of variations of atrioventricular conduction time unless they are grossly abnormal

With training and experience it is often possible to analyze the jugular venous pulse by inspection and to observe well marked delay in the interval between atrial and ventricular waves or to see completely blocked atrial waves falling in longer ventricular pauses The difficulty or impossibility of noting slight changes however and the likelihood of confusion even after training make graphic records—preferably electrocardiograms—essential for the establishment of the diagnosis of atrioventricular block in all but the most marked cases in which there happen to be actual dropped beats or very slow pulse rates (35 or less per minute) The phlebogram by measurement and the electrocardiogram at a glance show the presence and grade of block (Figures 36 page 167 and 164 page 935) Mechanical pulse tracings taken from cardiac apex or arm artery may rarely show the atrial pressure waves and the presence of block (Figure 31 page 158), but the chief value of the analysis of the ventricular action in arteriogram or cardiogram in heart block is in the finding of a dominant rhythm when there are dropped beats Without auscultation however this finding does not tell whether the pause is due to a true dropped beat or to a ventricular premature beat that has failed to show itself in the arterial pulse Moreover the varying conduction time that often occurs before and after a dropped beat shortens the pause and may be confusing in measurements of the arteriogram

Auscultation in atrioventricular block may sometimes reveal an extra sound usually faintly heard and often double due to the atrial contraction which may be separated sufficiently from the ventricular contraction to be clearly heard in a few cases This additional sound may come just before the normal first heart sound making the latter seem reduplicated or it may come well before it and if the heart rate is fast give rise to a presystolic gallop rhythm If there is considerable delay in conduction the extra sound may come in the middle of diastole early in diastole or immediately after the normal second heart sound giving rise respectively if the heart action is fast to middiastolic gallop rhythm protodiastolic gallop rhythm, or simple reduplication of the second sound (Chapter 5) Finally in heart block of high degree with dropped beats or in complete atrioventricular block the atrial contractions may be heard usually dimly at regular intervals between the ventricular contractions or they may at times coincide with the ventricular contractions causing an accentuation of the first second or third sound (Figures 13 and 14 in Chapter 5)

The heart rate in atrioventricular block is as a rule normal because there are generally no dropped beats and the atrial rate is unaffected With dropped

beats showing a higher grade of block the ventricular and peripheral pulse rates fall and tend at first to be irregular With 2 to 1 and complete heart block the heart rate falls to 40 30 and rarely somewhat lower Very marked slowing of the pulse down to 20 10 or even 2 or 3 beats a minute is rare and always very transient it is due to depression of the idioventricular pacemaker which does not take up the control of the heart when the atrial impulses are almost completely blocked off from the ventricles or else it is due to this same ventricular pacemaker depression coming on periodically in the course of complete heart block It is most common in the transitional stage between partial atrioventricular block of high grade and complete block before the idioventricular rhythm has become established When complete heart block is well established excessive slowing of the heartbeat though possible is rare It is the ventricular standstill with cerebral anemia occurring with this extreme slowing of the heart rate that is responsible for the syncopal attacks in the Morgagni Adams Stokes syndrome The slowest heart rate that has been recorded is one beat a minute (Odriozola 1920) but ventricular standstill of from 2 to 3 minutes with recovery has been reported also of course this must necessarily be a transient condition if it is more prolonged or often repeated death results The longest period of ventricular standstill proved electrocardiographically has been so far as I know 79 seconds following a period of over 3 minutes of abnormal ventricular tachycardia including ventricular fibrillation in this patient no pulse or cardiac contraction could be seen felt or heard for a period of 5 minutes recovery with two months more of life followed an injection of epinephrine directly into the heart (Levine and Matton 1926) The more recent notable case of a twenty minute cardiac arrest with complete recovery after cardiac massage apparently involved the whole heart (Adams and Hand 1942)

The reaction of the heart rate to various factors in the presence of atrioventricular block is of interest Often with lesser grades it increases normally with exercise and excitement but often even with lesser grades the reverse happens and the heart slows This paradoxical condition is due to the increase in the grade of block and number of dropped beats as a result of the increase in atrial rate the conducting tissue is no longer able to carry every impulse at the increased atrial rate so that 2 to 1 block develops with marked slowing of the ventricular rate while there is simply delayed conduction at only a moderately slow heart rate For example at rest both atrial and ventricular rates may be the same 72 per minute while on exercise the atrial rate may rise to 96 and the ventricular rate fall to 48 (2 to 1 block) The variation in atrial rate dependent on respiration may also in a critical case have a similar effect (Bourne 1928) this is particularly true in the case of Cheyne Stokes respiration Vagal stimulation by carotid sinus pressure and also the administration of digitalis may easily convert a slight grade of atrioventricular block into a high grade though rarely if ever complete

The blood pressure is unaffected in heart block unless the ventricular rate is very slow (about 30 per minute) when there tends to be a rather high

systolic pressure (150 to 160 mm) and a full pulse pressure (from 80 to 100 mm) this is a more or less compensatory condition and is due to increased filling of the heart during the prolonged diastole together with full emptying during the prolonged systole that always accompanies a slow pulse rate Considerable hypertension however in a case with complete heart block is always a complication and never a part of the circulatory mechanism of complete heart block itself

The blood flow at rest in atrioventricular block is not remarkable even at very slow heart rates because with a slow pulse the output of the heart per beat is almost correspondingly increased An output of 120 cc of blood per beat at a heart rate of 35 per minute gives a minute volume of blood flow of 4 2 liters not much less than that of the normal 4 9 liters at a heart rate of 70 and an output of 70 cc per beat With complete heart block however and to a less extent with partial block of high degree there is relatively little variation of the blood flow possible with exercise on account of the inability of the heart to increase its rate and because the ventricles are already putting out almost their maximum capacity per beat

Roentgen ray studies are of little or no help in the analysis of atrioventricular block although it is frequently possible to observe fluoroscopically the independent atrial and ventricular actions and when the ventricular rate is very slow to note the increased fullness of cardiac contraction with enlargement which may be entirely due to the increased diastolic filling

Electrocardiography is the only satisfactory method for the analysis of this disturbance of rhythm (Figure 164 page 935) it has also the great advantage of giving other evidence especially *T* wave changes of any very extensive or rapidly progressive coronary heart disease

There may or may not be signs of cardiac enlargement and failure valvular disease and hypertension Usually there are cardiac signs of some sort especially enlargement with the greater degrees of atrioventricular block

Course and prognosis Atrioventricular block is always important not so often in itself as in showing the existence of serious disease or toxic states This disturbance of rhythm is usually an incidental or accidental discovery in the course of routine health examinations or during the study of some illness cardiac or noncardiac It is discovered only very rarely at the time of its origin The only sign of its presence may be electrocardiographic or there may be the extreme signs and symptoms of block of high degree with the Morgagni Adams Stokes syndrome

In young persons not acutely ill with rheumatic or other infection the finding of atrioventricular block even of highest grades is compatible with good health and full activity for many years and even for long lives this seems to be particularly true of instances of congenital heart block that survive early childhood Even pregnancy has been normally carried through in cases of complete heart block with good reserve and little or no other evidence of heart disease In older persons new heart block is more serious even in slight grades unless digitalis is responsible for coronary disease of progressive character is

likely to be the cause and sometimes angina pectoris is associated with it When the heart block appears in the course of an acute infection at any age it adds somewhat to the gravity of the prognosis for it may mean serious cardiac involvement Rarely atrioventricular block may itself kill as the result of ventricular standstill Such a fate is usually ushered in by attacks of syncope the Morgagni Adams Stokes syndrome but this syndrome does not always end fatally it may occasionally be a temporary condition with complete recovery following the establishment of a stable complete heart block or very uncommonly a *return to normal rhythm to be followed by normal activity and* years of life

Complications The only important complications of atrioventricular block are gross myocardial infarction angina pectoris congestive heart failure the Morgagni Adams Stokes syndrome and intraventricular block the last named will be discussed later in the present chapter Congenital interventricular septal defects are the rule in the very rare cases of congenital heart block

Treatment Atrioventricular block rarely needs any treatment for itself but it frequently is associated with or due to some disease which does demand treatment especially rheumatic infection syphilis and coronary heart disease with myocardial infarction or angina pectoris Improvement of these conditions spontaneously or with the help of more or less specific therapy may be attended by a decrease or disappearance of the heart block A few striking cases of lessening of heart block in syphilis following specific therapy have been reported probably due to the clearing up of a gumma pressing on the atrioventricular junctional tissue or of an inflammatory condition of the tissues themselves Full salicylate therapy has been said to have reduced acute rheumatic heart block and the new hormone therapy with ACTH or cortisone is very encouraging (see Chapter 14) Rest and other treatment of angina pectoris have at times been followed by decrease in coincident heart block The high grade heart block that may appear paroxysmally for a few hours or a few days at the onset of myocardial infarction usually of the posterior wall of the left ventricle secondary to acute occlusion of the right coronary artery or of the circumflex branch of the left tends to clear up spontaneously without special therapy other than complete rest but its amelioration can be effected on occasion by the use of the nitrites especially erythrol tetranitrate 0 015 to 0 03 gm ($\frac{1}{4}$ to $\frac{1}{2}$ gr) every three or four hours Ample antitoxin therapy of severe diphtheria has been associated with recovery after the appearance of atrioventricular block Finally the treatment of congestive failure by digitalis in some cases complicated by atrioventricular block has even resulted in the reduction of the grade of block along with general improvement in spite of the fact that digitalis itself is sometimes alone responsible for heart block

If certain toxic agents like quinidine and digitalis are the cause of a serious grade of heart block they should be at once omitted if they produce but slight grades of block they may be discontinued or else reduced in amount careful watch being established that the block be not increased

In the presence of atrioventricular block not produced by some poison that

can be controlled some attention to the future health of the affected individual should be given even though there be no symptoms produced by the block or any evident heart disease Care should be exercised to avoid extreme fatigue overexertion and infections but otherwise there should be no restrictions or therapy, unless particularly indicated The finding of heart block especially in a young person needs in no way to render him a cripple but electrocardiograms and physical examination at intervals perhaps once every year or two are useful guides to the progress favorable or unfavorable of the state of the heart

Finally in rare instances it is necessary to treat the heart block itself when ventricular standstill is so frequent or of such long duration that cerebral symptoms develop dizziness faintness syncope and convulsions (Morgagni Adams Stokes syndrome) The most that can be done as a rule is to give therapy to prevent the attacks rarely an attack itself can be treated if it is of long duration and facilities are at hand The most effective measure in the prevention of the Morgagni Adams Stokes syndrome is the subcutaneous or intramuscular injection of *epinephrine (adrenaline) hydrochloride* 0 25 to 1 cc of the 1 1 000 solution (equaling 0 25 to 1 mg) at intervals of every few hours as needed (introduced by Hardoy and Houssay 1917 and by Phear and Parkinson 1922) Recently epinephrine in oil (2 mg of epinephrine hydrochloride in 1 cc of sesame or peanut oil) has been introduced in this prophylactic therapy with the advantage that because of its slow absorption under he skin only one or two injections may be needed in 24 hours when the effect is beginning to wear off massage of the site of injection will introduce some of the as yet unabsorbed epinephrine into the circulation This is almost invariably effective in preventing ventricular standstill either by decreasing the grade of atrioventricular block or more commonly by stimulating the activity of the idioventricular pacemaker The heart rate may be maintained above 30 per minute sometimes even as high as 50 for hours or days at a time by this therapy The atrial rate is simultaneously raised by the epinephrine to 90 or 100 or more Less effective immediately but more gradual and prolonged in its action and closely related in effect to epinephrine is *ephedrine* given in the dose of 15 to 30 mg (¼ to ½ gr) of the hydrochloride three to six times daily by mouth sometimes considerable nervousness results from its use Paredrine a similar drug has also been used with favorable effect given in the dosage of 40 to 60 mg by mouth three times a day (Nathanson et al 1942) Very rarely even digitalis may be tried if it keeps the s a rate from rising to critical levels above which serious a v block is set off Finally three other drugs have been given thyroid extract or thyroxin barium chloride and atropine sulfate Each of these drugs has sometimes succeeded but more often failed they are less effective than epinephrine and ephedrine and rarely worth bothering about

For emergency treatment of a prolonged period of ventricular standstill with syncope convulsions and apparently impending death the intracardiac injection (by long needle) of 0 1 to 0 5 cc of 0 1 per cent solution of epi

nephrine hydrochloride (i e 1 1 000) may be tried (though usually unsuccessfully) provided ventricular fibrillation is not itself the cause of the asystole electrocardiographic evidence of previous attacks of the Morgagni Adams-Stokes syndrome in the case in question is important Epinephrine may be lifesaving if administered within a few minutes of the cessation of the heartbeat but the drug is not without danger since it can itself induce ventricular tachycardia and fibrillation (Hoff and Nahum 1934) large dosage such as a full cc of 1 1000 epinephrine hydrochloride solution should for that reason be avoided

Differential diagnosis Atrioventricular block when there is simply delayed conduction can be differentiated with certainty from normal rhythm only by the electrocardiogram or by a good phlebogram When there are dropped beats heart block is to be differentiated from premature beats which are very early or very faint careful auscultation usually permits a clear distinction between the two Finally atrioventricular block of high degree must be distinguished from marked sinoatrial bradycardia or block which usually requires venous or electric tracings for diagnosis but which can at times be detected by trained observation of the jugular pulse The Morgagni Adams Stokes syndrome is to be differentiated from other cause of syncope and convulsions usually an easy matter because of the very slow heart rate or actual cardiac standstill the absence of paralysis the absence of a previous history of epilepsy nephritis diabetes and neurocirculatory asthenia and the presence of other signs of heart disease besides the block itself It is however important to note that high grade heart block may be wholly paroxysmal with normal *P R* interval between the relatively short periods of bradycardia or syncope Electrocardiograms or at least direct observation of the heart rate should always be secured during the actual attacks

INTRAVENTRICULAR (BUNDLE BRANCH) BLOCK

When there is depression of conduction in the branches of the atrioventricular bundle intraventricular or bundle branch block is said to exist Undoubtedly much of this intraventricular block is unrecognizable because either it is slight in degree in the larger branches or it affects only a limited number of the smaller branches of the conducting system (Purkinje network Purkinje 1845) When block exists to a moderate or marked degree in either of the two main bundle branches (right or left) or in a very extensive area of the finer network it becomes evident in the electrocardiogram but its presence cannot be proved in any other way It is better to speak of lesser grades of intraventricular block of left bundle branch type or of right bundle branch type or of uncertain type (slight aberration) than to use the term arborization block for it is as yet impossible to distinguish partial bundle branch block of either main branch from extensive block of the lesser branches

Incidence As is the case with slight grades of atrioventricular block intraventricular block is undoubtedly more frequent than statistics generally indi

cate since electrocardiograms are essential for its detection Intraventricular block of all grades is somewhat more common than atrioventricular block of all grades Of 10 000 cases electrocardiographed at the Massachusetts General Hospital during the fifteen years from 1916 to 1930 inclusive there were 734 cases of intraventricular block (7 3 per cent) and 641 cases of atrioventricular block (6 4 per cent) Of the cases of intraventricular block 223 showed full degrees or marked preponderance of left or of right bundle branch block and 511 lesser grades of block, the left bundle branch type was considerably more common than the right but not to the extent it was once thought to be before the introduction of the precordial leads or the recognition that a wide *S* wave in Lead 1 usually indicates a type or grade of right bundle branch block During the decade from 1934 to 1943 inclusive there were at the Massachusetts General Hospital 1 040 cases of clear-cut bundle branch block of either branch type 258 of which were right and 782 left

Mechanism (abnormal physiology) Bundle branch block may be due as in the case of atrioventricular block either to temporary functional or to permanent organic conditions but temporary or functional bundle branch block is very rare compared to both permanent bundle branch block and functional or temporary atrioventricular block Conduction when depressed in both main bundle branches equally may give rise to a condition that is indistinguishable from atrioventricular block but when one branch is more depressed than the other or some very extensive area of the finer arborizations is affected the lack of balance is shown in the electrocardiogram which simulates a dextrogram or a levogram If the left bundle branch is diseased or depressed so that the impulse is delayed in reaching the left ventricle spreading to the ventricular muscle wholly or in large part by the right branch the condition is called left bundle branch block and the electrocardiogram has the character of a dextrogram (Figure 165) when the right bundle branch conduction is grossly defective the ventricular deflections of the electrocardiogram resemble the levogram and right bundle branch block is present (Figure 166) The nomenclature is that based on the convincing work and conclusions of Mann and of Wilson and his associates and of others in recent years in opposition to the older point of view now largely discarded with its opposite nomenclature of bundle branch block

Wilson (1942) called attention to the reason for the earlier confusion based on the common dissimilarity of the curves of bundle branch block in man and in the dog The crux of the situation lies in the universally median vertical position of the dog s heart in contrast to the commonly diagonal or horizontal position of man s heart As Wilson says had direct or precordial leads been taken earlier the confusion need never have arisen

Between the two extreme conditions of full left and full right bundle branch block there are various grades and combinations of intraventricular block sometimes difficult accurately to analyze Intraventricular block is frequently found present when there are high degrees of atrioventricular block

The criterion for the diagnosis of bundle branch block is an abnormal

width or duration of the first ventricular complex that is the *QRS* wave provided the *P R* interval is not too short (that is not so little as 0 1 second or less) An upper limit of 0 1 second has been more or less routinely regarded as the borderline beyond which bundle branch block is to be diagnosed but it is undoubtedly true that on occasion the normal may exceed that slightly

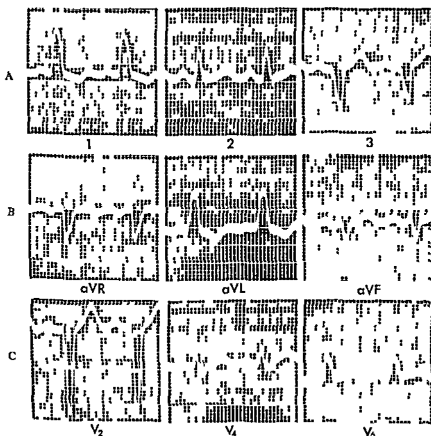


FIG 165 Electrocardiogram in left bundle branch block female age 68 (*A*) Bipolar limb leads 1 2 and 3 (*B*) unipolar limb leads aVR aVL and aVF (*C*) three precordial leads V V and V_6. Note the wide *QRS* waves throughout the left axis deviation in the limb leads and especially the notched and slurred *R* waves in Leads V and V_6. Time = 0 04 and 0 20 second amplitude 1 mm = 0 10 mv

(up to 0 11 second or even a shade more) and also that very large hearts (dilated hypertrophied or both) can have widened *QRS* waves (up to 0 12 second) without actual bundle branch block It is of some related interest that the very large *heart of the normal elephant has a wide QRS* wave of about 0 2 second and that the human infant s heart records a *QRS* wave of only 0 05 second Thus as in the case of the *P R* interval so too in judgment concerning the *QRS* wave much care must be used with full recognition of the

wide range of the normal heart (see Chapter 2), the electrocardiographic time intervals are to a certain extent at least a function of heart size

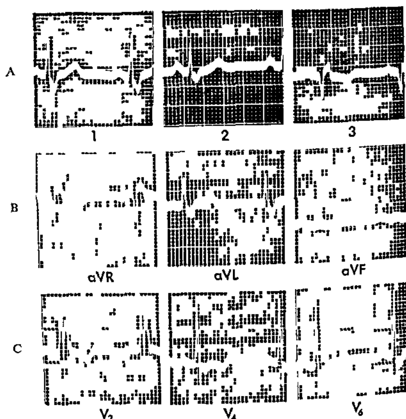


FIG 166 Electrocardiogram in right bundle branch block male age 60 (*A*) Bipolar limb leads 1 2 and 3 (*B*) unipolar limb leads aVR aVL and aVF (*C*) three precordial leads V V and V Note the wide *Q* waves in Leads 1 2 aVL and V_4, the wide *R* waves in Leads 3 and aVR and especially the wide M shaped *R* waves in Lead V Time = 0 04 and 0 20 second amplitude 1 mm = 0 10 mv

There may occur as in the case of most other disturbances of rhythm and conduction paroxysmal bundle branch block such a mechanism which may antedate by weeks or months a permanent change An interesting variation is 2 to 1 bundle branch block (see Figure 167)

Etiology *Cause* The commonest cause of bundle branch block is coronary atherosclerosis resulting in faulty nutrition degeneration and eventual fibrosis of the larger or smaller bundle branches Occlusion of a large coronary artery (more often the right or the circumflex branch of the left) or of the smaller vessels which supply the bundle branches may be followed by infarction involving right or left main trunks or lesser branches

There is a considerable discrepancy however between the occurrence of bundle branch block and the clinical evidence of coronary heart disease al though less than in the case of atrioventricular block In a series of 700 pa

tients with angina pectoris without myocardial infarction there were 7 7 per cent who showed intraventricular block (as compared to 1 5 per cent who showed atrioventricular block) while among 328 cases of myocardial in

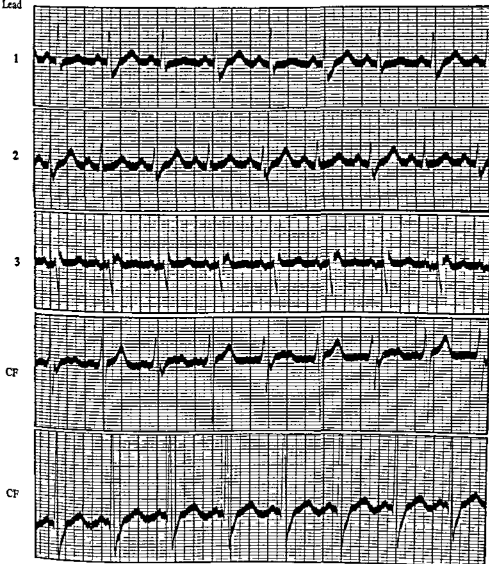


FIG 167 Alternating right bundle branch block in a man age 59 The alternation has cleared in Lead CF in which lead there is constant right bundle branch block Time = 0 10 and 0 20 second amplitude 1 mm = 0 10 mv

farction there were 9 5 per cent with intraventricular block (4 2 per cent had atrioventricular block) on the other hand among 181 cases of bundle branch block of all grades 39 1 per cent showed angina pectoris without myo

cardial infarction (29 8 per cent) or myocardial infarction with or without angina pectoris (9 3 per cent) (Salcedo and White 1935)

Other less common causes of organic intraventricular block are scarring from rheumatic myocardit s (preponderantly involving the right bundle branch) syphilitic infection in the heart (gummatous or diffuse) acute diphtheria (when it is especially serious and likely to be fatal) rarely other infections such as from viruses or bacterial endocarditis and very rarely tumors and trauma

Of a series of 52 cases of intraventricular block 44 or 84 6 per cent were thought to be due to coronary disease 3 cases (5 8 per cent) were apparently rheumatic 3 cases were syphilitic and 2 cases were of unknown cause (White and Jones 1928)

Functional intraventricular block transient in occurrence is relatively in frequent It has however been noted as a toxic result of too much digitalis or quinidine or of other poisoning It may occur as the result of fatigue in very rapid heart action, as temporarily in atrial flutter without atrioventricular block

Sex Males show bundle branch block much more commonly than do females probably because of a higher incidence of serious coronary disease The ratio is about 3 to 1

Age Bundle branch block is much more common in older persons 80 per cent of the cases being more than 50 years old It is very rare in infancy and early childhood

Pathology In a few cases of established intraventricular block no pathologic change is found in the bundle branches but it is probable that in most of these exceptions there is a limited blood supply because of coronary dis ease In instances in which some temporary poison fatigue from tachycardia or unusual vagus stimulation is responsible naturally no pathologic change is to be expected functional and organic factors may however be combined It is usual to find some changes especially fibrosis in the bundle branches in pronounced degrees of intraventricular block but the search in the human heart is a difficult one and much experience and patience are required for identification of the bundle branches and their careful study as yet there is insufficient information about their structural pathology A source of con fusion is that both bundle branches may show considerable pathologic change when the electrocardiogram indicates either left or right branch block or there may even be more change on the opposite side (Yater 1938) the ex planation is probably that the structural changes alone are inadequate to account for the whole picture and that a few conducting fibers on one side may be more effective than a large number on the other side for some reason per haps because of a difference in blood supply It is apparently rare for bundl branch damage or depression to be wholly unilateral

Symptoms There are no symptoms of bundle branch block There are fre quently associated however the symptoms of angina pectoris and congestive failure and palpitation due to various complicating arrhythmias

Signs There are no characteristic signs of bundle branch block except the pathognomonic electrocardiograms on which the diagnosis depends (Figures 165 page 947, and 166 page 948) There may be in some cases reduplica tion of one or of both heart sounds due to the somewhat asynchronous con tractions of the ventricles resulting from bundle branch block but this sign is not constant When both heart sounds are clearly reduplicated intraventricular block should be looked for

Usually heart disease is evident when there is bundle branch block Cardiac enlargement is a common finding but valvular disease is relatively infrequent. Hypertension occasionally exists and there may be signs of heart failure Roentgen ray examination is of no particular help

Course and prognosis Bundle branch block of slight degree may be a rela tively unimportant accidental discovery or it may be associated with serious and rapidly fatal heart disease such as extensive infarction from coronary thrombosis In some cases it exists unchanged for many years allowing full activity but in others it may change in the course of weeks or months increas ing in degree along with symptoms and signs of progressive heart failure It may be entirely unimportant in rare cases occurring as a more or less transient effect of vagal stimulation or of fatigue in excessive tachycardia Of itself it is not fatal but each case must be analyzed carefully Although the prognosis is to be based largely on other evidence of heart disease the finding of true bundle branch block of high degree renders the prognosis necessarily more guarded The average survival time for 281 cases of right bundle branch block was 3 9 years and for 555 cases of left bundle branch block 3 3 years (see below) The 185 cases of right bundle branch block who survived the first year of follow up had an average survival time of 5 7 years and the 356 cases of left bundle branch block who survived the first year had an average survival time of 4 9 years From these figures it would appear that the right bundle branch block may show a slightly better prognosis than left bundle branch block however an analysis of the survival time at different age groups indicates that after the age of 50 there is only slight difference between the average survival periods of right and left bundle branch block either in the total number of patients or in the group who survived the first year

There seem to be two general clinical groups of cases with bundle branch block (1) that with a rapidly bad prognosis based largely on the presence of evidence of extensive heart disease usually considerable enlargement and some degree of myocardial or coronary insufficiency and (2) that with a good prognosis of years of life and activity in which the bundle branch block is the only abnormal finding despite this general trend accurate prognosis in an individual case is often difficult It is the general finding at present that the cases with the lesser grades of right bundle branch block (wide *S* waves in Lead 1) survive the longest statistics are accumulating but are not yet fully adequate

Among others three series of cases of bundle branch block have been considered prognostically in recent years One series of 126 patients showed a high

mortality during the first year (60 cases nearly 50 per cent), 15 of the cases died during the next few years and 11 were still living 4 to 8 years after the discovery of the lesion neither the configuration of the electrocardiogram nor the duration of the *QRS* deflection seemed to be of prognostic significance (Kaplan and Katz 1939) On the other hand a series of cases reported by Perera Levine and Erlanger (1942) showed a considerably longer average survival time for right bundle branch block (3 years for 29 fatal cases) than for left (1 year and 2 months for 60 fatal cases) long time survivors in each group were still alive the longest exceeding 17 years for the right and 15 years for the left A third more recent series (Shreenivas et al 1950) referred to above has dealt with larger numbers over a longer interval A series of 281 cases of right bundle branch block electrocardiographed at the Massachusetts General Hospital gave the following statistical findings death within one year in 45 patients (16 per cent of the total series and 24 per cent of those traced) and survival of 72 cases for more than five years after the bundle branch block was discovered (27 per cent of the total series and 40 per cent of those who could be traced) In a consecutive series of 555 patients with left bundle branch block, also electrocardiographed at the Massachusetts General Hospital a survival period of less than one year was found in 170 (31 per cent of the total series and 32 per cent of those traced) and of more than five years after the bundle branch block was discovered in 121 (21 per cent of the series and 28 per cent of those who could be traced)

Complications There are no complications directly due to the bundle branch block unless in very rare cases both bundle branches are completely blocked with a resulting condition which is indistinguishable from atrioventricular block of this possible mechanism we have no definite clinical knowledge Conditions frequently complicating intraventricular block are atrioventricular block of all grades atrial fibrillation angina pectoris, myocardial infarction congestive heart failure pulsus alternans and hypertension

Treatment There is no direct treatment of the bundle branch block but therapy of any cause that may be recognized may not only help the underlying disease or disorder but also very rarely decrease or abolish the intraventricular block this may happen in the case of atrial flutter or paroxysmal tachycardia with functional bundle branch block and in syphilitic rheumatic or diphtheritic affection of the heart Complications such as congestive heart failure and angina pectoris should be treated without any regard to the presence of the bundle branch block

Differential diagnosis Bundle branch block must be differentiated from a normal ventricular mechanism and this can be done only by electrocardiogram electrocardiography also distinguishes the various types of intraventricular block as described above Even by electrocardiogram however it may be occasionally difficult in the presence of very rapid heart action to distinguish bundle branch block from ventricular paroxysmal tachycardia it may be necessary to wait till the pulse slows before differentiation is clear There is no particular condition pathologic or otherwise to be differentiated from

intraventricular block, except the anomalous state of the conducting system in which the impulse is transmitted with excessive speed to one ventricle or the other rather than delayed in the contralateral branch in such cases the $P R$ interval is excessively short and that is the clue that makes the differentia tion at once clear (Wolff Parkinson and White 1930)

WIDE *QRS* WAVE WITH SHORT *P R* INTERVAL

An odd electrocardiographic anomaly (Figure 168) probably congenital in origin has been found in healthy young persons prone to paroxysmal tachycardia (Wolff Parkinson and White 1930) it has the appearance of bundle branch block with short $P R$ interval (0 1 second or less) The wide *QRS* waves may on occasion spontaneously or after exercise or atropine sud

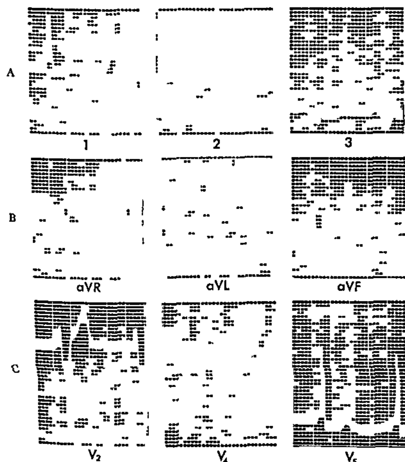


FIG 168 Electrocardiogram showing short $P R$ and wide *QRS* waves (Wolff Parkin son White syndrome) Male age 43 (*A*) Bipolar limb leads 1 2 and 3 (*B*) unipolar limb leads aVR aVL and aVF (C) three precordial leads V V and V Time = 0 04 and 0 20 second amplitude 1 mm = 0 10 mv

denly give way to normal *QRS* waves with normal *P R* intervals The total duration of the short *P-R* interval plus the wide *QRS* wave is well within normal limits and equal in the same subject to the duration of the normal *P R* interval plus the normal *QRS* wave to which the case may at times revert. A most certainly the correct explanation of this anomaly is that there is no bundle branch block at all and that the impulse travels much more rapidly than usual from atrium to one or the other ventricle either (1) by special conducting fibers from sinoatrial node or elsewhere in the atrium to one ventricle or the other (e g via a bundle of Kent Kent, 1893), or (2) by supernormal spread down one or the other bundle branch (thus representing a right or left *bundle branch acceleration* instead of the usual reversed left or right bundle branch block) or (3) less likely as the result of two interfering pacemakers one in the atria and the other in the ventricles (Hunter et al 1940) thus shortening the *P R* interval and giving rise to a *QRS* wave that in shape resembles that of bundle branch block, sometimes the impulse in any given case may pass through the short circuit and sometimes through the usual circuit in the bundle of His

Almost all the patients have remained in good health but a few have succumbed in middle or in old age to such complications as coronary thrombosis or even apparently to a disturbed heart rhythm (as in a recent case of our own a woman aged 48 who died suddenly during or after a paroxysm of atrial fibrillation with an excessive heart rate of 300 or slightly more) Autopsies in 2 or 3 cases have apparently revealed an extra bundle (of Kent) (e g Öhnell 1940) The syndrome is not very rare it makes up about 5 per cent of cases with wide *QRS* waves and about 5 per cent of patients subject to paroxysmal tachycardia (Hunter et al 1940)

SUDDEN DEATH

The most dramatic disorder of cardiovascular function is that which causes sudden death in fact it was such a source of concern to Pope Clement XI in Rome in the winter of 1705 to 1706 that he directed his physician Lancisi to study the problem by autopsies and otherwise and in 1707 one of the very few books on the subject was published by Lancisi Sudden death is apparently due to an abrupt ventricular asystole (from standstill or fibrillation) quite possibly with an additional element of sudden depression of the central nervous system No adequate reason may be found pathologically for such a death although there is usually evidence of considerable coronary or aortic disease consisting generally of marked sclerosis and narrowing of the coronary arteries or of syphilitic aortitis Sudden death is quite a different matter from the more gradual death from asphyxia in heart failure or from massive pulmonary embolism or from cerebral hemorrhage

Very few cases indeed are explained by cardiac or aortic rupture with abrupt exsanguination It is most likely that the effective mechanism of the heartbeat itself is suddenly stopped by a great reflex vagal effect with paralysis

of the pacemakers or by the onset of ventricular fibrillation Already a small group of electrocardiograms taken at the time of death under various conditions has been accumulated but we need many more With the solution of the mystery there may come progress leading to the resuscitation of some of these victims Epinephrine and other drugs injected directly into the heart and certain mechanical and electric stimulation such as massage during abdominal operations applied directly after rapid thoracotomy or from under the diaphragm the prick of a needle with or without electric charge or even striking the chest wall have restored the circulation in some individuals whose hearts had stopped beating Cardiac massage along with the maintenance of artificial respiration has proved the most consistent of the successful procedures to date (Dripps et al 1948) Further discussion of cardiac standstill and ventricular fibrillation and possible resuscitation therefrom can be found in Chapter 33 pages 919 to 921 and in this chapter pages 929 930 941 and 944

An important note should be added herewith to this discussion namely that rations of quinidine sulfate 3 gr four to six times a day may very possibly prevent the onset of ventricular tachycardia and fibrillation that leads to rapid death in some cases of fresh myocardial infarction or of a high degree of coronary insufficiency as indicated by angina pectoris decubitus (Borg 1939)

There has been in recent years a revival of interest in the pathologic findings on postmortem examination of persons who had died suddenly I shall summarize four such analyses Martland (1940) has told of his own experience with the autopsies of 2 000 individuals over the age of ten whose deaths were sudden but not the result of violence the majority were between 40 and 65 and by far the larger number were males (1 680 or 84 per cent) Organic heart or aortic disease was present in 1 590 (79 5 per cent) 8 per cent had disease of the respiratory organs 4 per cent of the head and the remaining 8 5 per cent were subjects with miscellaneous conditions Of the 1 590 cases of disease of heart or aorta 1 115 (55 per cent of the total 2 000) were of the coronary or hypertensive type 262 had syphilitic aortitis 116 rheumatic heart disease and 97 other types of heart disease Among the coronary cases which numbered 731 (36 5 per cent of the total) there was coronary occlusion with acute thrombosis in 304 and without acute thrombosis in 314 the remaining 113 cases showing considerable atheroma without actual occlusion of the larger vessels Well marked aneurysm of the left ventricle was present in 59 cases and rupture of the ventricular wall in 42 persons Large hearts without much coronary disease and probably the result of hypertension occurred in 384 cases Among the 262 syphilitics aneurysm of the aorta was found in 102 cases aortic regurgitation in 70 and stenosis of the coronary ostia in 80 Rupture of the aorta had occurred in 37 persons of the total series Aortic stenosis was found in 32 cases and pulmonary embolism in 10 There was one young colored man who showed at autopsy no abnormalities whatsoever marked apprehension about an impending minor surgical procedure immediately preceded his sudden death and it was thought that this was an almost

unique example of an overwhelming nervous (vagal) depression of the heart beat with resulting death from fright'

Analysis of another group of 123 autopsies in cases of unexplained sudden death (Jeckeln 1940) showed two thirds to have been the result of heart disease with coronary lesions forming the great majority, six times more often in men than in women Excessive filling of the stomach with food was frequently found in these fatal coronary cases In 7 cases death was due apparently to syphilitic aortitis and 5 cases had aortic stenosis while only 1 had mitral stenosis (with coronary sclerosis) In 2 cases death resulted from rupture of the aorta and in 3 others from apoplectic cerebral hemorrhage Ruptured aneurysm at the base of the brain (giving rise to a subarachnoid hemorrhage) was found in as many as 19 cases There were 30 cases of sudden death in children 6 of which were stillborn the others being due to a variety of infections traumatic brain lesions sustained at birth and acute respiratory disorders

Lisa (1939) noted the findings in 41 persons dying sudden cardiac deaths acute coronary thrombosis was present in 10 acute coronary insufficiency was apparently responsible in 5 more acute endocarditis was found in 5 rheumatic heart disease in 4 syphilis in 8, and pulmonary lesions in 2 5 cases were infants or children and the remaining 2 were entirely unexplained

More recently Helpern and Rabson (1945 and 1947) have reported their experience These authors have analyzed in considerable and interesting detail 2 030 consecutive cases of sudden and unexpected death in the Borough of Manhattan from January 1937 to July, 1943 Table 14 below gives the details of this analysis 912 cases or 44 9 per cent involved the heart and aorta 468 cases or 23 1 per cent involved the respiratory tract 367 or 17 9 per cent involved the brain and meninges 198 or 9 7 per cent involved the digestive and genitourinary tracts There were 90 miscellaneous cases or 4 4 per cent If we include cases of pulmonary embolism and of cerebral vascular accidents with the cases of heart and aorta to complete the cardiovascular responsibility we have a total of 1 195 cases or 59 0 per cent The greatest incidence of all these cases was in the decade from 45 to 54 years of age inclusive Males were preponderant over the females in a ratio of 4 to 1 Among the coronary cases 80 per cent died instantly Also among the coronary cases three fourths showed no grossly fresh thrombosis

In closing this chapter and the book itself may I suggest that after all neither a high even 100 per cent mortality from cardiovascular disease nor sudden death itself are to be regretted provided they take place at an advanced age after a healthy and happy and useful life right up to the last minute In fact this is actually an ideal goal toward which man may strive for it means the eradication not only of other diseases such as the infections of the past and the cancers accidents and the wars of the present but also the control of the serious cardiovascular threats (such as hypertension and coronary atherosclerosis) to the lives of our youth and middle aged which bid fair to trouble

us for still some years to come Furthermore we physicians must work hand in hand in our labors with our pioneering colleagues in the gravely needed advances in the social economic and spiritual fields of human endeavor Those of us who have striven during the last generation to probe a little into the depths of our ignorance can turn over with confidence to our successors the far more important task of bringing to pass the aim expressed in the first sentence of this closing paragraph

Table 14

ANALYSIS OF 2 030 AUTOPSIED CASES OF SUDDEN AND UNEXPECTED NATURAL DEATH[1]

Groups	*Individual Diseases*	*Number*	*Percentage of Group*	*Percentage of Total (2 030)*
Heart and Aorta 91[illegible] Cases (44 9%)	Coronary artery disease	617	67 7	30 4
	Syphilitic aortitis	107	11 7	5 3
	Valvular disease	83	9 [illegible]	4 1
	Cardiac hypertrophy	35	3 8	1 7
	Spontaneous rupture of aorta	[illegible]5	2 7	1 2
	Others	45	4 9	[illegible]
Respiratory 468 Cases (3 1%)	Lob r pneumonia	176	37 6	8 7
	Bronchitis bronchopneumonia	133	8 4	6 5
	Pulmonary tuberculosis	68	14 5	3 4
	Pulmonary embolism and infarction	31	6 7	1 6
	Others	60	1[illegible] 8	2 9
Brain and Meninges 367 Cases (17 9%)	Cerebral hemorrhage	110	30 4	5 4
	Subarachnoid hemorrhage	93	[illegible]5 7	4 6
	Cerebellar hemorrhage	11	3 0	0 6
	Pontine hemorrhage	11	3 0	0 6
	Cerebral thrombosis and embolism	7	7 5	1 3
	Meningitis	38	10 6	1 9
	Brain tumor	[illegible]9	8 0	1 4
	Others	43	11 8	2 1
Digestive and Urogenital		*198*		9 7
Miscellaneous		90		4 4

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When the cause of the hyperglycemia is apparent it is suggested that it should not be called diabetes mellitus but instead be referred to as the hyperglycemia of that particular disease state. Thus one would speak of the hyperglycemia of Cushing's syndrome or of acromegaly and confine the term diabetes mellitus to those conditions in which the hyperglycemia is of uncertain or unknown etiology.

History.—The disease was well known to the ancients. Aretaeus in the first century used the word diabetes, named from the Greek word meaning a syphon. Due to the polyuria dominating the picture Galen thought that the kidneys allowed fluid to "run through" without alteration. In India the sweetness of the urine had been recognized for many centuries before Dobson, in 1775, obtained a sugar by evaporation. This sugar was later proved to be the same as that in grapes by Chevreul in 1815. Little further advance was made until von Mering and Minkowski in 1889 to 1892, produced the diabetic state in dogs by extirpation of the pancreas. For many years investigators the world over attempted to produce a nontoxic pancreatic extract that would have a specific effect upon the blood sugar of the diabetic dog. Little success was attained until in 1921 the work of Banting and Best, with the chemical assistance of Collip, proved the possibility of preparing such a pancreatic extract containing the desired active principle. This hormone has been named *insulin*.

Incidence.—Although diabetes is a common disease in many countries it is difficult for several reasons to arrive at an accurate estimate of its true incidence. It is usually considered that a fair reflection of the incidence of a possible fatal disease may be obtained from its death rate. But in the case of diabetes this record does not represent the total number of people with this disease who die. In the first place the primary cause of death in a diabetic may be recorded as tuberculosis, cancer, heart disease, etc., and second it may be considered as an incidental finding because the diabetic state is not recognized or because the doctor may be consulted in the terminal stage of some other illness and not have an opportunity to uncover the diabetes. The death rate from diabetes per 100,000 in the United States has increased from 9.7 in 1900 to 26.4 in 1944 but from 1940 to 1944 it has remained practically stationary (26.6 compared to 26.4). Joslin estimates that this represents at the most about two thirds of the people with this disease.

The total number of persons with diabetes in the United States (and proportionately in Canada) is variably estimated from 460,000 to 725,000. But Joslin, taking into consideration that in only two thirds of the death certificates of diabetics is the disease recorded, estimates that there were probably at least 1,000,000 diabetics in the United States in 1946.

It must not be taken that the incidence of the disease is uniform throughout the population. There are a number of conspicuous divergencies of which the following are the more important and here the death rates will be taken as the index. The death rate per 100,000 varies with age. It increases in progressive decades as the following will show. In 1941 to 1945 the death rate under 25 was 1.5, between 25 and 44 it was 4.4, and from 45 to 74 it was 89. Furthermore, there has been an actual change in these relations over

recent years as in 1911-1915 the rates were 3.0, 7.2, and 63.7, respectively. This realignment has been due to two factors, namely, since the introduction of insulin therapy there has been a conspicuous reduction in diabetic mortality in persons under 50 and particularly in children; furthermore, the death rate and the incidence of diabetes rests within the individuals in the upper age groups. Therefore, as the life expectancy has increased since 1900 from 48 years in males and 51 in females to 63 and 68, respectively, in 1943, there are more people in the age groups where diabetes is most frequent. This relative increase in these people has been further accentuated by the prolongation of life due to insulin. It must not be inferred from this that diabetes is an old person's disease. The age at death might seem to indicate this, but Joslin has pointed out that the age of onset is under 50 in 57 per cent of males and 49 per cent of females, and in approximately 23 per cent the onset is between 30 and 50 years of age.

Sex.—*At the turn of the century the reported incidence in males was definitely* greater (roughly two to one) than in females. During the past fifty years this ratio has practically been reversed. Joslin attributes this to two principal reasons: (1) the greater attention being given to the health of women and (2) the increase in the number of women in the upper decades. This change not only holds for the United States but for most countries of the world.

Race.—The high incidence of diabetes amongst the Jewish race is well known. It has also been shown that the age of onset is earlier than in the general population. What is not usually appreciated is its relatively high incidence amongst the Irish in the United States as compared to the rate in Ireland. Joslin attributes this to the fact that the general well-being and prosperity of the Irish in North America is much higher than in Ireland itself and further that during the time covered by his studies a disproportionate *number of the Irish engaged in the liquor business. Bose has pointed out that* in Bengal amongst the large well-educated classes, in 2,000 cases 68.2 per cent were Hindus, 14.6 per cent Mohammedans, 2.1 per cent other castes, and 15.1 per cent Europeans. But he does not take into account the relative populations. However, he further records for Calcutta an over-all increase of rate per 100,000 of 5.2 in 1929, 10.4 in 1933, and 20.7 in 1934. This startling increase would seem to be due to some factor other than an etiological one, such as better diagnosis. Mills has, on the other hand, reported a low incidence of this disease in China and quoted others on its rarity and mildness in Japan and the Philippines, India in general, Sudan, West Africa, and Venezuela. The clue to these variations is suggested to be an etiological one of prosperity and overindulgence in food and drink, as intimated by Joslin for the Irish. It has also been found that the incidence of diabetes is higher in the urban as compared to the rural population. This would tempt one to make a generalization that the incidence of this disease is greatest in countries where the urban population predominates and the standard of living is high.

Etiology.—As stated by the earlier investigators, heredity still stands today as the basis upon which diabetes rests. There are other factors such as obesity and infections which play a contributing part.

betics was unable to demonstrate any microscopic changes in the pancreatic islets in 20 per cent of the patients. Although it was recognized that histological appearance may not be an adequate criterion of the functional status of an endocrine gland, this observation directed attention to other possible causes of the metabolic disturbance associated with this disease. That other factors might be involved was also indicated from a comparison of the insulin requirements of patients rendered diabetic by complete pancreatectomy with those who have spontaneous diabetes mellitus. The former usually require no more than 30 units of insulin daily for adequate control of the blood glucose level, while patients with spontaneous diabetes frequently require more.

Although in most patients with diabetes mellitus it cannot be proved that insulin deficiency is the primary cause, in some cases it can be inferred that destruction of the pancreas leading to insulin deficiency is responsible for the hyperglycemia. Of those diseases of the pancreas that may result in diabetes, the most important are the following:

1. Acute and chronic pancreatitis
2. Carcinoma
3. Hemochromatosis
4. Syphilis (a very rare cause)

In those cases of diabetes mellitus in which the primary cause might be an extrapancreatic factor, insulin deficiency may still play an important role in the continuation of the diabetic state. Evidence for this statement is provided by the recent experiments of Dohan and Lukens, which demonstrated that the injection of glucose to normal cats for some weeks resulted in sufficient degeneration of the islet cells so that in spite of discontinuation of glucose administration the diabetic state persisted. These observations indicate that hyperglycemia per se can produce islet damage and insulin deficiency, and support the view that in the treatment of diabetes mellitus one of the important objectives is the maintenance of the blood sugar within normal limits.

From this discussion it is apparent that in those cases of hyperglycemia of unknown etiology, i.e., diabetes mellitus, there is as yet no convincing proof that insulin deficiency is the primary cause of the carbohydrate disturbance. *However, it must be emphasized that, regardless what the cause may prove to be, from the point of view of practical management these patients should be looked upon as being unable to provide a sufficient amount of endogenous insulin to meet their metabolic requirements.*

ADRENAL. The hormones of the cortex and the medulla affect the metabolism of carbohydrate. The administration of certain adrenal steroids (those with an oxygen atom on carbon 11 of the steroid nucleus, such as Kendall's compound E) to rats results in a diabetic state characterized by marked insulin resistance. That overproduction of adrenocortical steroids can also produce hyperglycemia in man is indicated by the high incidence of hyperglycemia (approximately 90 per cent) in patients with Cushing's syndrome. Further evidence that the adrenal is primarily responsible for the diabetic state in such patients is the fact that when the disease is associated with an

adenoma of the adrenal cortex its successful removal is almost invariably followed by a disappearance of the hyperglycemia In patients with diabetes mellitus who do not have Cushing s syndrome there is at present no convincing evidence that overactivity of the adrenal cortex is an etiological factor

The frequent association of hyperglycemia with pheochromocytoma which disappears with resection of the tumor indicates that the overproduction of epinephrine is effective in elevating the blood glucose But there is nothing to suggest that the medulla of the adrenal gland is responsible for the carbohydrate disturbance in diabetes mellitus

PITUITARY There is abundant evidence to indicate that certain of the hormones of the anterior pituitary gland play an important part in the regulation of carbohydrate metabolism That overproduction of such hormones may be responsible for the development of a diabetic state is a possibility which is supported by the experimental production of hyperglycemia in animals by the administration of suitable pituitary extracts Such extracts can produce experimental diabetes in at least two ways one of which is mediated through the adrenal cortex Thus the hyperglycemia which follows the administration of pituitary adrenocorticotrophic hormone is a consequence of increased production of adrenocortical hormones while that which follows the administration of the so called diabetogenic hormone " is not (Young)

The Coris have shown that the carbohydrate active anterior pituitary extracts depress the activity of the enzyme hexokinase in vitro Since the action of this enzyme is essential for the normal utilization of glucose this is probably the mechanism by which the diabetogenic extracts of the pituitary produce hyperglycemia It is of considerable importance that this inhibiting effect which is enhanced by the adrenocortical steroids is neutralized by insulin

More direct evidence that the anterior pituitary gland may play some part in the etiology of human diabetes mellitus is provided by the recent observations that the administration of pituitary adrenocorticotrophic hormone to normal human subjects results in the temporary production of hyperglycemia and glycosuria At present however the anterior pituitary can only be invoked in explaining the hyperglycemia which is associated with acromegaly Both the incidence (approximately 30 per cent) of hyperglycemia in such patients and the amelioration which frequently follows resection of the acidophilic adenoma are strong evidence that the hyperglycemia in these patients is due primarily to increased secretion of pituitary hormones In some cases the diabetic state may continue even when the tumor appears to have entered an inactive phase In such cases the continuation of the diabetic state may be the result of a secondary insulin deficiency as described under the pancreas These clinical findings have a counterpart in the experimental animal since Young has succeeded in producing hyperglycemia which persists after cessation of injection of pituitary extracts This persistent hyperglycemia is associated with lesions of the islet cells which are probably secondary to the pituitary induced hyperglycemia

THYROID Although the thyroid hormone may play some part in regulating the blood sugar concentration it has not been possible to produce per

manent hyperglycemia experimentally by the administration of this hormone. However, the incidence of hyperglycemia in patients with thyrotoxicosis is two to three times that in the general population. The correction of hyperthyroidism in such patients often results in an amelioration of the diabetic state, and it seems likely that the overproduction of thyroid hormone is responsible for intensifying a latent or mild diabetes but is not the primary cause.

Liver.—The liver normally plays an important part in the metabolism of carbohydrate. It stores the ingested carbohydrate as glycogen which it later converts to glucose in order to maintain the blood glucose concentration in the fasting state. It also is the chief site where noncarbohydrate substances are converted to glucose (gluconeogenesis). Since the storage of glucose as glycogen in the liver is one of the important ways by which the organism avoids an excessive elevation of the blood glucose following a meal, it has been suggested that a failure of this to occur might result in hyperglycemia. It is undoubtedly true that some patients with hepatic dysfunction which may be associated with say cirrhosis may have an impaired carbohydrate tolerance which manifests itself usually as a postprandial hyperglycemia. As yet there is no evidence to indicate that hepatic insufficiency plays an important role in the etiology of the diabetic state except in those patients with overt hepatic disease. Since the liver occupies a central position in the homeostatic mechanisms which regulate the concentration of blood glucose, it will not be at all surprising if future work reveals that hepatic dysfunction is important in the etiology of diabetes mellitus.



Fig. 319.—[illegible] of fibrotic pancreas from a case of diabetes in a middle-aged person [illegible] following a gallbladder tract infection.

Psychosomatic Factors.—There is scant if any evidence that emotional disturbances play any role in the etiology of diabetes per se. On the other hand, such conditions may act on the pancreas to reduce insulin production or even on the pituitary to increase the diabetogenic hormone. There is ample evidence to indicate that such traumata increase the severity of the diabetic state and that larger amounts of insulin may be required during the period of their operation. It would not be surprising, therefore, if a latent diabetic state became florid under such conditions and might be accused of being a primary etiological cause (see Chapter XVI).

Pathological Anatomy.—The absence or variability of pathological findings *in the pancreas at autopsy has always been a* "stumbling block" in establishing the functional disturbance upon an anatomical basis. The child diabetic who

dies in coma rarely shows much histological alteration in the pancreas unless it be a general collapse of the organ The middle aged diabetic whose diabetes is secondary to a gallbladder tract infection frequently shows marked fibrosis with extensive loss of acinar and islet tissue (and sometimes considerable small round cell infiltration) Such cases have had repeated attacks of sub acute pancreatitis *In the aged diabetic the commonest alteration is a total* atrophy of the pancreas with little relative alteration in either acinar or islet structure *There are usually mild grades of interacinar sclerosis*

An important contribution that has led to a changing conception of pan creatic pathology was the proof that the islands were capable of regeneration Previously the pancreas in the diabetic state was viewed as an organ not capable of regenerative capacity but slowly undergoing degenerative changes

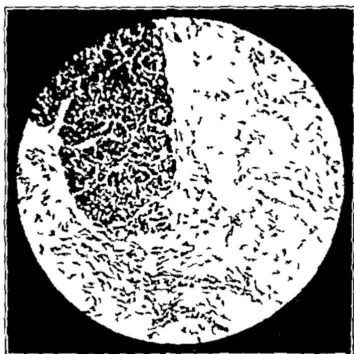


Fig 320 —Photograph of a microsection of the pancreas in Fig 319 showing extensive fibrotic replacement of pancreatic tissue

Recently a more labile conception has come to the fore, which views the changes as a result of the balance between regenerative and degenerative forces With this conception one could imagine a toxic factor acting through out the history of the disease leading to degrees of hyaline degeneration and ultimate fibrosis with loss of function of the islands of Langerhans Antago nistic to this the regenerative capacity of the organ may result in the formation of new islet tissue Since its regenerative capacity is so slow one would not expect to find active evidence of the same The course of the disease is ulti mately determined by the balance between these two forces This conception explains best the pathological alterations found in the elderly diabetics In many young diabetics one would have to accept the hypothesis that function

can be greatly suppressed without histological alteration In the middle aged diabetics, usually secondary to gallbladder tract infections, there is a chronic pancreatitis due to an inflammatory reaction initiated and in some cases maintained, by bacterial or chemical causes Normal bile when injected under low pressure into the pancreatic duct may produce a mild but transient edema and round celled infiltration about the ducts If infected bile is similarly injected, there is set up an intense necrosis It has not been proved whether this is due directly to the bacteria or their toxin, or to some chemical change which they have produced in the bile

Pathological Physiology—Since the diagnosis of diabetes mellitus is established by demonstrating that the concentration of blood glucose is excessively high it seems logical to discuss the disturbances in carbohydrate metabolism which exist in this disease from the point of view of those factors which regulate or alter the blood glucose level

Blood Glucose—Normally the concentration of glucose in the blood is maintained within narrow limits The regulation of this normal level is complicated and is dependent on the normal activity of the gastrointestinal tract, liver and the endocrine glands particularly the pancreas anterior pituitary and adrenal cortex

At any given time the level of blood glucose will depend on the rate at which glucose enters the blood stream and the rate at which it is removed Stated in a different way it may be said that the blood glucose level is a balance between the rate of its formation and the rate of its utilization In the fasting state these are so adjusted that the glucose concentration is normally 80 to 100 mg per 100 c c During periods when carbohydrate is being absorbed from the gastrointestinal tract the blood glucose concentration will rise Since the rate of carbohydrate absorption from the intestine is essentially independent of the amount ingested and the mechanisms for the removal of glucose from the blood stream are very efficient the blood sugar concentration rarely reaches a level higher than 140 to 160 mg per 100 c c in the normal individual This peak concentration is usually attained 30 to 60 minutes after the meal The blood glucose is usually back to the fasting level in 120 to 150 minutes

In the fasting state in normal individuals the arterial and venous blood sugars are practically the same After eating a spread develops between the two greatest at the peak values and gradually declining to the postabsorptive state The difference is due to the removal of glucose from the capillary blood and at the peak values may amount to 60 mg per 100 c c The mild diabetic shows practically the same arteriovenous difference as the normal The more severe the diabetes the less is the difference due to the failure to remove glucose from the capillary blood This is best shown in the digestive period Absence of difference in the digestive period is strong evidence of a diabetic state

Hyperglycemia—Since the level of blood glucose is dependent on the rate of its formation and on the rate of its utilization hyperglycemia may be due to overproduction of glucose or to its underutilization or to a combination of the two

Glucose is utilized in three principal ways (1) oxidation to carbon dioxide and water (2) conversion to liver and muscle glycogen and (3) conversion to fat *The oxidation of glucose is enhanced by insulin while it is inhibited by the carbohydrate active hormones of the anterior pituitary gland and the adrenal cortex* Insulin also enhances the conversion of glucose to glycogen and fat

In the postabsorptive state glucose is formed from liver glycogen and from noncarbohydrate sources notably protein *and the glycerol of fat by a process known as gluconeogenesis* Insulin inhibits gluconeogenesis while the anterior pituitary and adrenal cortical hormones stimulate it

It is apparent then that the hyperglycemia associated with acromegaly and Cushing s syndrome is due to both overproduction and underutilization of glucose In the majority of patients it is likely that the latter mechanism *is the more important one*

Since insulin enhances the utilization of glucose and inhibits its production the hyperglycemia associated with insulin deficiency could be due to either or both of these mechanisms At present the evidence favors the mechanism of underutilization This also appears to be the case in those patients with diabetes mellitus of unknown etiology

By *virtue of diminished utilization of glucose the blood glucose will reach* a higher level in a patient with diabetes mellitus than in a normal individual after the ingestion of carbohydrate If immediately following a meal the venous blood glucose exceeds 160 mg per 100 c c a state of hyperglycemia may be said to exist If the underutilization is severe enough the blood sugar will be elevated *in the fasting state* as well Values *of 100 to 120 mg are of* doubtful significance while a concentration of more than 120 mg per 100 c c of blood is usually considered to signify hyperglycemia

The Glucose Threshold in Diabetes —

Glycosuria —Glycosuria is one of the important consequences of hyperglycemia since it is responsible for many of the symptoms and signs of the disease In addition the demonstration that glucose is present in the urine is often the first indication that the patient may have diabetes mellitus The *mechanism of the excretion of glucose in the urine has been elucidated through* the researches of Richard

It would seem to be well established that the glomerular fluid is a mechanical filtrate through Bowman s capsule from the capillary blood and that it contains glucose in the same percentage concentration as the blood in the *afferent vessel coming to the glomerulus As this glomerular fluid passes down* the convoluted tubules its glucose is reabsorbed Glycosuria will occur when the amount of glucose presented to the kidney tubules for reabsorption exceeds their reabsorptive capacity The amount of glucose presented to the kidney tubules will depend on the plasma arterial concentration of glucose and the volume of glomerular filtrate formed *In the normal individual the maximal amount of glucose which can be reabsorbed in one minute is 350 mg* In Fig 321 it will be seen that when the blood glucose level reaches 300 mg per 100 c c with a normal rate of glomerular filtration the glucose load to the kidney *becomes 390 mg in one minute* Since the maximal reabsorptive

capacity is 350 mg., the patient will excrete 40 mg. of glucose in the urine in one minute. It is really incorrect to refer to glycosuria in terms of "renal threshold" because this implies that the occurrence of glycosuria is only dependent on the blood glucose concentration. From the discussion above, it is apparent that at least two other factors are important, namely, the rate of glomerular filtration and the tubular reabsorptive capacity for glucose. However, the term is firmly entrenched in the literature of diabetes and will be retained in the discussion which follows.

It can be demonstrated by the most sensitive method of analysis that the normal urine contains a trace of glucose, indicating that this small amount escapes reabsorption. This "glycuresis" varies from 300 to 900 mg. of glucose per day and its percentage concentration is not great enough for the alkaline copper solutions to detect it (Benedict's, Fehling's, or Haines' solutions). The diabetic's glucose threshold has the same mechanism of action and the glycosuria that is present is dependent *in toto* upon the elevation of the blood sugar above the threshold. This threshold level is usually considered to vary from 160 to 180 mg. per cent for venous blood. The glucose threshold may be lower or higher than the average normal. On the low side one sees all levels finally merging into those found in renal glycosuria. The author has followed a case for over ten years with a constant threshold of 70 mg. per cent. It is also well established that the threshold may be raised. This elevation occurs in cases of long standing diabetes and especially in those with a progressive arteriosclerosis. Venous blood sugar values of 300 mg. per cent without glycosuria are not rare. The finding of a low threshold does not rule out diabetes. The diabetic state is quite independent of the threshold. The lower the threshold the greater the percentage excretion of glucose in the urine provided the urinary volume and the level of hyperglycemia are relatively constant. Many diabetics have a lowered threshold (120 to 150 mg. per cent venous blood) which is only discovered after the hyperglycemia has been controlled by treatment. If a raised glucose threshold in the kidneys is present the absence of glycosuria may fail to indicate the degree of hyperglycemia.

In Fig. 321 there is a schematic representation of the mechanism of the so called "raised" and "lowered" threshold. In diabetic patients with renal arteriosclerosis, because of a diminished rate of formation of glomerular filtrate the glucose load presented to the kidney may be less than the tubular reabsorptive capacity in spite of an elevated blood glucose concentration. Therefore glycosuria may not occur even when the blood glucose is 300 mg. per 100 cc. In patients with renal glycosuria, on the other hand, the glucose load is normal, 130 mg. in the example shown, but the ability of the tubules to reabsorb glucose is impaired and as a consequence glycosuria occurs in the presence of a normal blood glucose concentration. Thus if the tubular reabsorptive capacity was decreased to 80 mg. there would be a glycosuria of 50 mg. in one minute.

The determination of the glucose threshold in the kidneys can only be made upon the venous blood during the fasting state. This is essential because the threshold is an index of the arterial blood sugar level and only in the fasting state are they the same. If there is glycosuria in a controlled hourly

specimen taken in the early morning, the urine and venous blood sugar can be followed at hourly intervals until there is no glycosuria If there is no glycosuria in the fasting urine it is necessary to use capillary or arterial blood to obtain the true threshold Arterial or capillary blood sugars followed at half hour intervals and coordinated with corresponding urine samples after the administration of 50 grams of glucose by mouth will reveal the threshold Ideally the proper way to determine whether a low or high 'threshold' exists is to measure the exact glucose load presented to the kidney This involves the measurement of the glomerular filtration rate An approximation of this can be obtained as suggested by Corcoran by estimating the urea clearance It has been claimed that there is a difference between the threshold with rising and falling blood sugars This is not demonstrable when judged from capillary blood values. This confusion has arisen by attempting to judge thresholds using venous blood after the administration of glucose by mouth

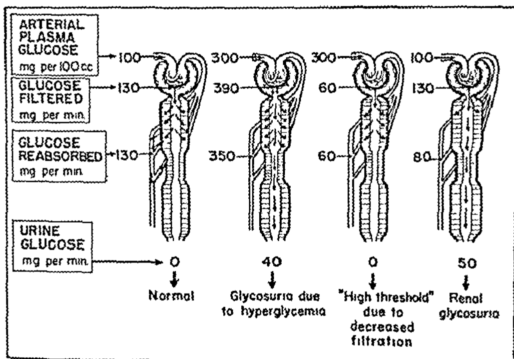


Fig 3 3 —(Court sy A C Cor ran Cleveland Clinic Quarterly October 1948)

Relationship of Carbohydrate and Fat Metabolism —The tissues prefer to oxidize carbohydrate rather than fat If the former capacity is impaired a greater proportion of the total calories produced will be derived from fat oxidation If fat oxidation is complete the end products are CO_2 and H_2O If incomplete the ketone bodies B hydroxybutyric acid (CH_3-CHOH-CH_2-COOH) acetoacetic acid (CH_3-CO-CH_2-COOH) and acetone (CH_3-CO-CH_3) accumulate in the blood and extracellular lymph and a type of acidosis called ketosis results Probably these ketone bodies are derived from butyric acid

(CH_3-CH_2-CH_2-COOH), a 4 carbon atom molecule in the normal oxidative catabolism of the higher fatty acids. The accumulation of ketone bodies in the blood of the inadequately treated severe diabetic is apparently the result of an overproduction of ketone bodies rather than to their diminished utilization. The ketone bodies are formed in the liver and although the precise reason for their overproduction in the diabetic patient is not known, it is likely that the depletion of liver glycogen and the infiltration with fat is responsible for the rapid breakdown of fatty acids into ketone bodies. Ketone bodies can also be derived from certain of the amino acids. Any substances capable of yielding these ketone bodies are called ketogenic. Glucose, derived from carbohydrate, or from certain amino acids of protein, or from the glycerol of neutral fat is said to be antiketogenic. Shaffer has attempted to develop a ratio of ketogenic to antiketogenic substances which, if the tissues exceed in their oxidative functions, would result in a mild ketosis. He stated his ratio to be 2 molecules of ketogenic acid to 1 of glucose. Later a ratio of 1 molecule of ketogenic acid to 1 of glucose has been shown to be more nearly correct. These ratios are influenced by many factors. The child and pregnant woman have lower ratios than the adult. Further, the tissues of an individual can acquire a greater capacity to oxidize fatty acids, while less glucose is oxidized without ketonuria. With carbohydrate diets containing 150 grams or more, there is no danger of ketonuria provided the carbohydrate ingested is oxidized.

In severe diabetes and especially in diabetic coma marked degrees of lipemia may be present. This can be diagnosed by examination of the fundi or by withdrawal of a sample of blood. Upon standing a cream-like layer separates out above the red blood cells which are rapidly sedimented. Values of 12 to 13 per cent of total lipoid concentration in the blood have been reported (normal 0.5 to 0.7 per cent). The cause of this lipemia is related to an increased fat transport via the blood stream, and is always associated in diabetes mellitus with hyperglycemia. With control of the diabetic state it rapidly disappears.

Cholesterol is one of the body lipoids but not a true fat. Very little is known about its exact intermediary metabolism. Its source is the food where it is closely allied to neutral fat. Internal organs, meats, eggs and butter contain the highest percentages. Uncontrolled diabetic states with hyperglycemia usually have hypercholesterolemia (normal plasma cholesterol 150 to 250 mg. per cent). Values of 500 mg. per cent are not uncommon while in coma figures ranging from 500 to 700 mg. per cent may be present. With establishment of control the cholesterol falls much slower than the blood sugar and when it remains persistently elevated the prognosis is poor. Joslin has found that low blood cholesterols of 90 mg. per cent or under are of more serious prognostic significance than high values.

Great interest is being taken in the relationship of persistent hypercholesterolemia, and the development of arteriosclerosis. Certain authors have been of the opinion that high fat diets which frequently are associated with elevated blood cholesterol tend to produce arteriosclerosis. With the intro-

duction of the low fat high carbohydrate diet there has followed a very definite drop in the average of the blood cholesterol

Relationship of Carbohydrate and Protein Metabolism.—Carbohydrate is the greatest sparer of protein oxidation. By high carbohydrate feeding in normal persons the protein oxidized can be reduced to a minimum (about 19 grams per 24 hours). Provided sufficient carbohydrate is available, muscular work is performed at the expense of carbohydrate, the protein metabolism remaining unchanged. The diabetic having an impaired ability to oxidize carbohydrate calls upon his endogenous protein to supply needed calories. This call is greatest in the severe cases and especially if fat oxidation is incomplete, resulting in a ketosis. The degree of tissue destruction occurring can be accurately determined by the nitrogen excreted in the urine and feces, due allowance being made for the exogenous nitrogen in the food (6.25 grams of protein yield 1 gram nitrogen). Loss of weight is rapid where tissue protein destruction is pronounced. Insulin increases the ability of the diabetic to oxidize glucose and permits the protein metabolism to return to normal.

Insulin and Its Action.—In 1921 Banting and Best, with the assistance of Collip, working in Macleod's laboratory in Toronto, prepared an active pancreatic extract which was capable of lowering the blood sugar. This substance was named insulin. It was not until 1925 that it was isolated in crystalline form by Abel and Geiling. The chemical formula $C_{45}H_{5}N_{11}S$ has been assigned to it. Its content of tyrosine, arginine and histidine is high, and it contains a sulphur compound similar to cystine. It is capable of forming salts with acids. Insulin is found in practically all body organs, especially the pancreas and muscles, but the yield per gram of material is greatest from the pancreas and its commercial preparation is limited to extraction from this organ.

The normal individual is constantly receiving a supply of insulin from the pancreas. It is carried by the blood stream to all nucleated cells of the tissues. There it plays an essential part in the storage of glucose as glycogen and the oxidation of glycogen. Without insulin the oxidation of glucose in the muscles may be practically reduced to zero. Evidence would indicate that the tissues contain some unknown factor which is essential for the oxidation of glucose, since *in vitro* insulin will not oxidize glucose even in the presence of oxygenated blood. Insulin will also restore the normal spread between the arterial and venous blood sugars absent in the severe diabetic. This would indicate greater glucose removal from the capillary blood. The hormones of other ductless glands (pituitrin, thyroxin and adrenalin) exert a direct or indirect antagonistic action to insulin, the resulting blood sugar level being a balance between the two forces.

Insulin is available for clinical use in varying strengths and is standardized in units. One clinical unit is one third of the amount of insulin necessary to lower the blood sugar of a 2 kilogram rabbit kept under standard feeding conditions to the convulsion level. The amount of glucose that one unit of insulin will oxidize varies inversely as the severity of the diabetic state. Roughly one unit of insulin will burn from 1 to 6 grams of carbohydrate

Symptoms and Signs.—The concept of the clinical pattern of diabetes has changed radically in the last thirty years. This has been due almost entirely to a ready method of determining the blood sugar. In fact this statement is equally applicable to diagnosis and to treatment. Before such a test was available it was practically only those cases with the florid symptoms of thirst, increased appetite, polyuria, and weight loss with accompanying glycosuria that were so diagnosed. As we know now, a great majority of diabetics in the upper age brackets do not have these symptoms and were therefore overlooked in spite of the fact that glycosuria was present, or as this was often intermittent or varied considerably from time to time, its significance was not sufficiently

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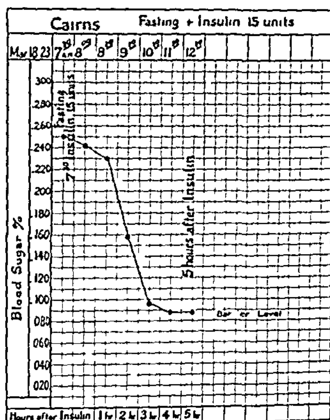


Chart XXIV.—The effect of insulin upon the blood sugar in the fasting state.

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Symptoms.—POLYURIA. The first complaint in the classical symptomatology of diabetes mellitus is usually polyuria. The detailed causation for this has been the subject of considerable controversy. It is therefore important to trace the sequence of events backwards from this point. The urine is clear in color with high specific gravity in proportion to the amount of its glucose content and also in amounts parallel to the latter. The volume may amount

to 5 or 10 or more liters per 24 hours the larger portion being passed in the daytime In the classical cases this polyuria is in proportion roughly to the degree of hyperglycemia It is obvious that with a high blood sugar the amount of glucose in the glomerular filtrate will be conspicuously increased As this is a threshold substance it would be expected that the amount of glucose reabsorbed by the tubules would be considerable but there is probably a limit beyond which this vital function may be ineffective in consideration of the high glucose content of the plasma on the other side of the tubular membrane Therefore the tubular content cannot be deprived of glucose to the almost complete extent as occurs under normal conditions Hence the glycosuria? But yet there is an excess of water left in the tubular content or urine One could postulate that the amount of urine should be reduced in order that the glucose isotonicity of the tubular vascular blood content would be maintained as nearly to a normal level as possible This would be an almost vain attempt in the florid cases or episodes in this disease (see below) On the other hand one might speculate that the pituitary or mid brain centers are sensitive to hyperglycosuria and so affect the diuretic factor as to increase its influence on renal tubular function There is another possible explanation which is a positive one related to the first but contrary postulate above This is that the tubular blood supply is saturated with glucose that the tubular content or urine withdraws water into the tubules since the concentration of glucose there is greater than in the blood stream or on the other hand prevents its transference inwards and so the polyuria This matter has not been clarified by experimental means For instance dogs have been continuously infused with glucose solutions producing a glycosuria of 12 to 13 per cent At such levels 1 gram of glucose carries with it only 6 to 8 c c of water Frequently a diabetic excretes as much as 12 c c or more of water for each gram of glucose But it must be appreciated that such dogs are not diabetic and more nearly approach the normal person who after a heavy carbohydrate meal easily rids himself of a small overflow of carbohydrate or the person with a low glucose renal threshold who passes glucose in the urine with a normal blood glucose level and no diuresis But there is no insulin deficiency and this factor has not yet been sufficiently explored to reach a conclusion as to the relative importance of a high glucose glomerular filtrate with a normal systemic blood sugar or a high systemic blood sugar and a normal glomerular filtrate *but an impaired tubular function* *The last would not seem to be of much im*portance in the present concept as in the nephrotic stage of glomerulonephritis in lower nephron nephrosis etc (see Chapter XVIII) glycosuria is not a feature

The fact remains from a practical clinical standpoint that in the florid *pattern of diabetes in children* young adults and occasionally in the upper decades polyuria may be the presenting symptom but in many of the latter unfortunately it is not sufficient to require the patient to seek professional advice and so the diabetic state passes unnoticed for an indefinite time

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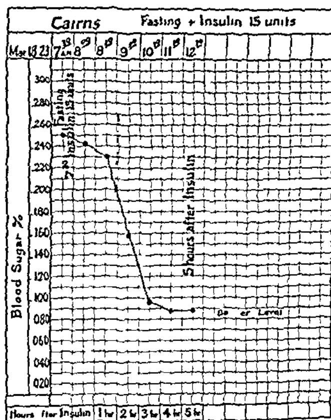


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the same in the extracellular tissue fluids as in the plasma. It has been postulated that there is a shift of water from the cells to the body fluids, resulting in tissue dehydration. But this still remains to be proved. If one takes the erythrocytes as a representative where the glucose content is in equilibrium with the plasma, there is no detectable difference in the formation or function under these conditions. Therefore, it is hard to believe that a fundamental shift of the cellular water balance leading to occult cellular dehydration is the cause of the thirst and consequent polydypsia. It seems much more logical to postulate for the present that this is a direct result of the polyuria. It is a well known fact that pronounced hyperglycemia and glycosuria without polyuria can be present without thirst or polydypsia.

POLYPHAGIA. In the classical clinical pattern of diabetes, polyphagia or hunger is a prominent symptom. The cause of this is not far to seek. The first action of insulin is to act on the liver in the storage of glucose as glycogen. This in turn on demand is released for use by the muscles and all other functioning organs. In the second place, insulin is of essential importance in the utilization by the tissues of the released glucose from liver glycogen. Therefore if the ingested glucose cannot be stored and utilized, other sources such as proteins and fat within the body are called upon to supply the demand which in turn are utilizable after a normal manner. So in conformance with a common law of a deprivation there is an increased desire on the part of the organism for an unusual demand. It is of importance to note in this regard that the diabetic craves carbohydrate in a concentrated form, which will be seen later to be one of the hazards of therapy in uncontrollable cases. So the polyphagia or gluttony of this type of diabetes is due to a failure of storage and utilization of carbohydrate, in which manner a large proportion of the caloric value of ordinary meals is lost and is manifested by the degree of glycosuria.

LOSS OF WEIGHT. This might be considered a secondary complaint in the symptomatology of classical diabetes and in the whole picture it is a paradox. It would seem obvious that the loss of weight is primarily due to inability of the liver to store glycogen and the tissues to utilize it. If appreciable potential calories are excreted in the urine in the form of glucose, the tissue will oxidize an equivalent amount derived from fat and protein. If the tissue protein is oxidized in a marked degree the weight loss will be rapid. A calculation will show that this is about eleven times more rapid when an equivalent number of calories is being derived from protein than from fat. The weight loss referable to dehydration is of minor importance.

It has been mentioned above that obesity is often a precursor to diabetes, particularly in the older age groups. This may remain present or even increase over the years if the caloric intake is excessive. Herein lies an unexplained paradox. On the other hand some patients lose weight, and parallel with this the diabetic process improves.

Other symptoms of less frequent occurrence are pruritus vulvae, weakness and constipation. The pruritis may be generalized and is usually associated with dehydration and heavy glycosuria. Drying of the urine on the vulva may cause a local irritation which is not uncommonly the symptom

for which the patient seeks medical aid Pruritus vulvae of this type will disappear promptly when the glycosuria has been controlled More rarely the pruritus vulvae is associated with a local mycotic infection Possibly the urinary glucose serves as a favorable culture media Such cases require special treatment Weakness as a symptom of diabetes is in proportion to the loss of weight Constipation is probably a matter of withdrawal of water from the intestinal tract Very few controlled diabetics eating vegetables and fruits are constipated

For years it was considered usual for patients with diabetes to complain of varying degrees of pain in their limbs and to show signs of neuritis The hyperglycemia was blamed as the cause Recent investigations have suggested the probability of a vitamin B_1 deficiency A large percentage of diabetics with neuritis have partial or complete achlorhydria which may have an etiological relationship to the vitamin deficiency

Signs—The physical examination of a diabetic patient is completely void of any signs diagnostic of the disease However one finds varying degrees of dehydration and dryness of the skin and minor skin infections are common Evidence of weight loss may be present The neurological examination may show absence of the prepatellar tendon reflex in almost 50 per cent of the untreated cases This sign is rare in the young

Clinical Classification—The fact that the diabetic state is not fixed makes it very difficult to classify in any satisfactory way The divisions, mild, moderate and severe as judged by the patient s ability to oxidize glucose are probably the most satisfactory

Mild cases are those not requiring insulin but are satisfactorily controlled by diet alone *moderate* cases require 30 units or less of insulin per 24 hours while *severe* cases demand more than 30 units Proper diabetic control means approximate freedom from glycosuria absence of ketonuria and a diet sufficient in calories to maintain weight One must not forget that a case may change from one group to another as a loss or gain of tolerance takes place This fluctuation of tolerance partly rests in the hands of the doctor and can be influenced greatly by proper diet insulin dosage and exercise In the main diabetes in childhood unless carefully supervised tends to become severe while after 60 years of age the disease is usually fundamentally mild

On the other hand diabetes may be classified as insulin sensitive and insulin insensitive In the first class there would be included all those cases of what might be called idiopathic diabetes which readily respond to insulin therapy and so are supposed to be due to a primary deficiency of the pancreatic internal secretion The second group do not respond to insulin and the cause can usually be traced to an abnormality in some other system or organ (see page 810)

Complications

Cardiovascular Disease—The etiology of arteriosclerosis is unknown Its incidence at the onset of diabetes varies directly as the age of the patient When not present at the onset it develops earlier in diabetics than in other patients It is rare to see a middle aged patient who has had diabetes for ten years

without some degree of calcification of the arteries Even with the onset of diabetes in childhood x ray signs of calcification may appear in the third decade The author has seen a diabetic, male, aged 27 years, with an eleven year history, who had extreme systemic arteriosclerosis with gangrene of one

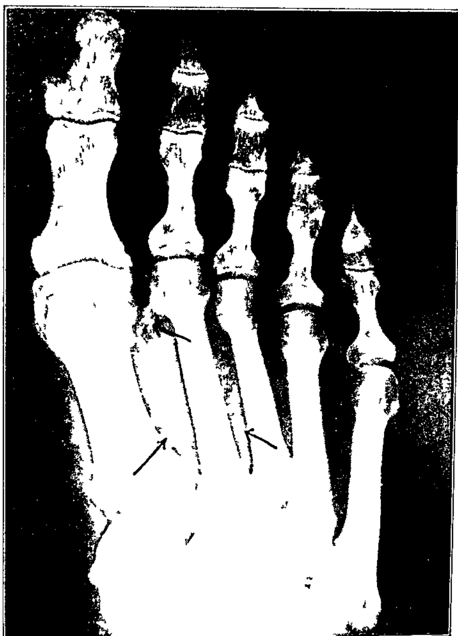


Fig 3 —X ray of the foot in a case of diabetes showing calcification of the arteries

toe The present evidence would indicate that excess lipoid in the blood contributes to the production of this arterial lesion Virchow showed that the intima of the larger arteries contained excess lipoid in arteriosclerosis This lipoid is a cholesterol ester which is later bound to calcium Any state that results in an excess blood lipoid concentration such as obesity or a high fat diet, would tend prematurely to develop this arterial lesion

There is little fundamental difference between the arteriosclerosis in diabetics and in nondiabetics Our experience has been that the arteriosclerotic process expresses itself as a degenerative change in the media with hyaline fusion and often calcareous deposits There is also marked intimal thickening and narrowing of the lumen with frequent occlusion by thrombosis *The medial change corresponds to the so called Monkeberg type* of arteriosclerosis, but this is believed to be due to the size of the vessel involved rather than to any essential difference from ordinary arteriosclerosis

Gangrene—Gangrene of the lower extremities is a common complication in diabetics It usually involves one or more toes but may develop in the tarsus as well It is due to death of tissue from lack of blood supply It is dry or moist according to the presence of secondary infection The so called "diabetic gangrene" differs from nondiabetic gangrene only in its tendency to infection and rapidity of spread As it spreads the surrounding tissues become reddened edematous and streaks of lymphangitis appear Frequently a small infection at the corner of a nail or under a corn or callus is the initiating factor for the onset of gangrene Given the two conditions hyperglycemia and impaired circulation gangrene is a potential danger

The lower extremity that has a grossly impaired circulation will show marked atrophy of the skin of the foot with loss of subcutaneous tissue Shiny skin is stretched over the bones like a mummy Pulsation in the dorsalis pedis and posterior tibial arteries cannot be palpated and the x ray may show varying degrees of calcification of the vessel walls (Fig 322) It is possible to have poor circulation with no sign of calcification while on the contrary there may be good circulation with pronounced calcification of the arteries as shown by x ray Surface temperature measurements after a spinal anesthetic or lumbar sympathetic block and the histamine flare test may be of value in special cases *The most important single criterion of the efficiency* of the circulation upon which depends the capacity of a gangrenous area to heal is palpable pulsation in the dorsalis pedis vessel next in significance is the state of atrophy of the skin and subcutaneous tissues The degree of calcification revealed by x ray is an unreliable guide

Arteriosclerosis of Other Organs—Next in importance to involvement of the legs is sclerosis of the coronary arteries leading to myocardial infarction The retinal vessels show changes rather early progressing to hemorrhages and exudate the so called diabetic retinitis

To any one who follows diabetics over many years a striking feature is the large number who develop a progressive failure of renal function due to vascular changes in the kidneys The diabetic state frequently becomes milder and there is a parallel depreciation of renal function Death takes place from uremia This has now been identified with intercapillary glomerular sclerosis (see Chapter XVIII) Cerebral thrombosis and cerebral hemorrhage are the causes of death in many with advanced cerebral arteriosclerosis

Infections—Some think that the diabetic is susceptible to infections on account of hyperglycemia Clinically it is our conviction that the controlled diabetic has not an increased susceptibility to infection The healing of

cases recover. Likewise pulmonary abscess can be given a good prognosis if satisfactory drainage can be established.

Diabetes and Pulmonary Tuberculosis.—Before insulin (1922) the prognosis of the diabetic with active pulmonary tuberculosis was extremely grave. Today the situation is not hopeless. A great deal depends upon the intelligence and the care of both the patient and the doctor. An illustration of what can be accomplished in some cases at least is that of a young woman who is now 40 years of age in whom diabetes was first recognized in 1919. Due to extreme conscientiousness on her part, she survived on a weighed diet to receive insulin in 1922. Subsequently her level of nutrition was built up to normal standards. For a time she became careless with her diabetic control and during this period she contracted pulmonary tuberculosis. In 1933 she had an active pulmonary lesion with positive sputum, and the x-ray showed conspicuous involvement of the left upper lobe. A diet of protein 70 gm., fat 50 gm., and carbohydrate 325 gm. required 96 units of insulin per day. Partial collapse of the affected lung was maintained for twelve months. The sputum became negative and in one year all clinical and x-ray evidence of the activity in the pulmonary lesion had disappeared. Today she is enjoying almost a normal life with a diet of protein 70 gm., fat 50 gm., and carbohydrate 275 gm., and 58 units of insulin a day.

There is little doubt that the diabetic is more susceptible to a tuberculous infection becoming active than the nondiabetic. This susceptibility is not great in the controlled diabetic, but is very appreciable in the uncontrolled case. The juvenile diabetics are much more susceptible than the adults. Great care should be exercised over diabetic children to avoid all contact with open tuberculosis and routine x-rays should be taken of their lungs at yearly intervals. The use of B.C.G. vaccine in those children who are Mantoux negative should be seriously considered.

Acidosis (Ketosis).—

Nature of Chemical Disturbance.—Diabetic acidosis is due to the incomplete oxidation of fatty acids. When this oxidation reaches the stage of the 4 carbon atom butyric acid the two ketone acids B-hydroxybutyric acid and acetoacetic acid are formed from which acetone is derived. These ketone acids pass into the blood stream and are converted into sodium salts at the expense of the $NaHCO_3$ present. Thus as their formation increases there is a greater exhaustion of the main base reserve. With the formation of the salt $NaHCO_3$ is broken down liberating $CO_2 + H_2O$. The CO_2 leaves the body via the lungs. If the base reserve is exhausted a shift of the pH of the blood follows and death takes place. Chemically the severity of the acidosis is indicated by the CO_2 capacity of the blood plasma. When treatment is instituted and carbohydrate is oxidized by insulin, the production of these ketone bodies ceases and those that are present are either oxidized or excreted.

	PLASMA CO_2 CAPACITY
Normal	55 to 65 vols %
Mild acidosis	35 to 45 vols %
Moderate acidosis	25 to 35 vols %
Severe acidosis	Below 25 vols %

When oxidized the base sodium is liberated and unites again with CO_2 to form $NaHCO_3$ with the restoration of the base reserve. Many cases of coma will show no alteration of the blood sodium throughout the total period of their recovery.

Recently attention has been directed to the importance of potassium depletion in diabetic coma. In coma there is an excessive phosphaturia which decreases the labile organic phosphates in the blood and tissues. This is further accentuated by the diuresis which results from excessive glucose and fluid therapy. The blood potassium may be reduced to such a degree as to cause muscular paralysis, particularly dangerous to respiration, and the electrocardiogram will show the typical changes of the S-T complexes associated with hypokaliemia.

Symptoms and Signs.—The symptoms characteristic of severe acidosis are air hunger (Kussmaul), flushed appearance, and dry skin. The pulse is rapid and the eyeballs are soft. The tongue is dry, and there may be vomiting with at times epigastric pain. A CO_2 capacity below 16 volumes per cent is usually associated with unconsciousness. The air hunger is characterized by deep and rapid respirations and is the most constant single symptom in a severe ketosis. It is probably due to the stimulation of the carotid body by the fatty acids, although it helps to reduce the C_H of the blood by elimination of CO_2 through respiration. Lipemia and an increase of blood cholesterol may be found during coma but it is usually temporary and has no prognostic significance. Dehydration accounts for the dry skin and dry tongue. The flushed appearance may partly be a matter of increased circulation rate as indicated by the pulse, and in part due to a decreased amount of reduced hemoglobin in the venous blood (note its bright red color) due to the increased O_2 content of the alveolar air brought about by the hyperventilation and also an increased circulation rate. The decreased intraocular tension is due to withdrawal of water from the vitreous. Vomiting is readily relieved by gastric lavage, which would indicate a local rather than central cause. The epigastric pain in some cases would appear to be due to a subacute pancreatitis.

The breath of the patient is fruity in odor due in part to acetone. The urine shows glucose, acetoacetic acid, and acetone. There is a hyperglycemia and a ketonemia. Children in diabetic coma with vomiting and abdominal pain frequently show great rigidity of the abdominal wall and a marked leucocytosis. Thirty to forty thousand white cells is not unusual, and one case occurred in this clinic with 52,000. The leucocytosis is of the polymorphonuclear type, and the count rapidly returns to the normal level as the acidosis is cured. These cases are often confused in diagnosis with acute peritoneal infections.

Effect of Acidosis Upon Carbohydrate Tolerance.—We have never been able to detect any permanent impairment of tolerance following diabetic coma (ketosis). One of our patients with an onset of diabetes at eleven years had thirteen attacks of coma during the first five years of her illness. She is now twenty-six years of age. There was only a very temporary impairment of tolerance following each attack. At no time was her growth arrested, and puberty was only slightly delayed.

Other Complications —

Gallstones and Gallbladder Disease —Cholecystitis and cholelithiasis are common findings in the middle aged, obese, diabetic woman The biliary tract infection usually precedes the appearance of the diabetic state, and is probably the primary cause of it Infected bile has been proved to be capable of causing a pancreatitis and these diabetics frequently have recurring attacks of subacute pancreatitis Cholecystitis is potentially more dangerous than cholelithiasis Provided the diabetic state has not been present for more than three months drainage or removal of the gallbladder as indicated may result in marked improvement of carbohydrate tolerance



Fig 3 —Xanthoma Diabeticorum (Courtesy of Dr Phillip Frank Shaffner From Sutton and Sutton Diseases of the Skin)

Xanthoma Diabeticorum —With the use of lower fat and higher carbohydrate diets xanthoma diabeticorum has almost disappeared The yellowish tubercles which appeared especially in the skin, were composed of fat cells in a connective tissue stroma with a deposit of cholesterol crystals in their centers They appeared more frequently upon the extensor surfaces at the points of slight trauma or friction Rarely were they generalized over the whole body These patients had hyperglycemia lipemia and marked hyper cholesterolemia (500 to 1000 mg per cent) With diabetic control the tubercles rapidly disappear leaving small whitish scars in the skin Increase in

the blood cholesterol of the same order is encountered in the nephrotic state but xanthomatosis does not occur

Cataracts—Anthonisen has shown statistically that there is a very significant association of cataracts with diabetes. They were fifteen times as common as expected in the age group between sixty and seventy four and 202 times as great as expected between twenty five and thirty. Cataract in juveniles does occur but it is not common and develops early in the disease.

Hypertension—Reference has already been made to the frequency of arteriosclerosis in diabetes mellitus but it does not necessarily follow that the former is the cause of hypertension in this disease. It is generally accepted that hypertension is more common in diabetics than in corresponding age groups of nondiabetics but there are some who do not agree with this. However of the anatomical lesions found at autopsy arteriosclerosis is first and cardiac hypertrophy second. This would seem to bear witness that hypertension is a common complication of diabetes mellitus.

Intercapillary Glomerulosclerosis—Reference will be made to this on page 1275. Although this is a comparatively rare condition the relatively high incidence of associated diabetes is significant. This is most common in young persons with diabetes of long duration.

Retinopathy—Retinopathy occurring in diabetics has long been recognized by ophthalmologists. In fact they differentiate a distinct type of the lesion associated with this disease. It is significant however that there is commonly but not always hypertension present also that the cause of death in many of these cases is nephritis or cerebral or coronary artery lesions. There is no doubt that the presence of retinopathy is of serious prognostic import at all ages.

Diagnosis

It has been stated above that diabetes mellitus may be present without exhibiting any symptoms or signs. On the other hand the onset may be sudden and the disease may progress to an advanced stage in a comparatively short time. For the sake of clarity the diagnosis will be considered under three groups.

1 The florid type of case offers little difficulty where the patient complains of any or all of the following—polyuria thirst polyphagia weight loss with abundant glycosuria. A blood sugar curve would confirm the diagnosis. However some of these symptoms may be present in other diseases as in hyperthyroidism or anxiety states with or without glycosuria and to make a definite diagnosis a hyperglycemia of a diabetic character must be present.

2 The accidental finding of a reducing substance in the urine in a routine examination as when seeking insurance offers more difficulty. It is well to determine the exact nature of the reducing substance by fermentation osazone formation or by the polariscope. If it turns out to be a true glycosuria a blood sugar curve is indicated. This should be done after the patient has been on an adequate diet high in carbohydrate for three days as a low diet over a period of time so affects the liver as to permit a high blood sugar curve to be present. However a fasting blood sugar above 140 mg per cent

is certain evidence of the diabetic state, as all nondiabetic causes of glycosuria have normal fasting blood sugar levels except acromegaly, Cushing's syndrome and pheochromocytoma. If glycosuria is present with a normal fasting blood sugar level, hyperthyroidism, acromegaly, Cushing's syndrome, hepatic lesions, intracranial lesions and renal glycosuria must be considered. In all incipient or doubtful cases the glucose time curve is most important and if there is still any uncertainty when this is done with venous blood as is customary, then a curve done with capillary blood after immersion of the arm in hot water may be of the greatest value.

3. In some elderly patients who complain of either an unexplained increase or decrease in weight, *furuncles or a carbuncle, or peripheral gangrene* (particularly of the toes) but without apparent glycosuria, diabetes should be suspected. As persons in the upper decades often have a high renal threshold for glucose, glycosuria may not be present in a single specimen of urine. It is well to control such a possibility with a fasting blood sugar estimation in the first instance and follow it by a blood sugar curve if there be any doubt.

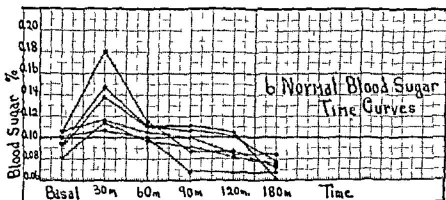


Chart XXV —Six normal blood sugar time curves. Note the constancy of the peak at thirty minutes but the [illegible] the prompt return to the base line and the subsequent depression below the fasting level.

The Glucose Time Curve.—The glucose time curve is a synchronous observation of the blood sugar and the urine sugar starting in the fasting state and continued over a two to three hour period after the administration of 50 to 100 grams of glucose by mouth. The blood sugar curve so obtained reflects the efficiency of the balance of those forces tending to elevate and those forces tending to lower the blood sugar. Since there is a maximum rate of absorption of glucose from the stomach and upper intestine, excess administration of glucose only tends to prolong the absorption period. Fifty grams of glucose give the same blood sugar curve as 100 grams. Most clinics have used the latter amount.

The normal individual shows the peak of the blood sugar rise in thirty minutes with a return to normal in sixty to ninety minutes. Subsequently the blood sugar falls below the fasting value to return to it in the third to the fourth hour. There is no glycosuria. The height of the peak is of little importance provided the drop is precipitous and reaches the fasting level on time. The character of the normal curve is dependent upon an active secretion of insulin which is initiated by the rising blood sugar. This insulin accelerates the storage of glycogen mainly in the liver which more than offsets

absorption Thus the blood sugar starts to fall and a peak is formed The rate of fall is largely an index of the rapidity of glycogen storage The mild hypoglycemic level from the second to the third or fourth hours is due to storage rather "overdoing" itself for a limited period of time The peak of arterial blood sugar normally ranges from 160 to 200 mg per cent while the venous ranges from 140 to 160 mg per cent

The diabetic glucose time curve characteristically shows four abnormalities The more severe the diabetes is (1) the higher the fasting blood sugar (2) the higher and more delayed the blood sugar peak (3) the longer the blood sugar takes to return to the fasting level and (4) finally the presence of glycosuria during the period that the arterial blood sugar exceeds the threshold Only the very mildest diabetics show any hypoglycemic response

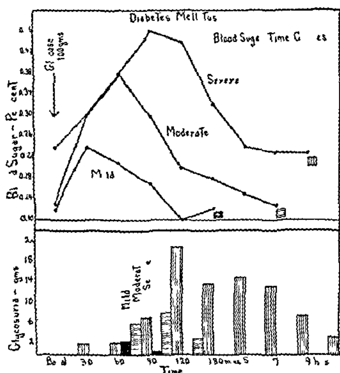


Chart XXXI—Glucose time curves in the case of diabetes of varying severity Note the more severe the diabetes the higher the fasting blood sugar the more delayed the peak and the slower the return of the blood sugar to normal

Undue *prolongation of the hyperglycemic phase is usually considered* to be more important than the height of the peak The severe diabetic will show a quantitative relationship between the amount of glucose taken and the degree of hyperglycemia which also controls the glycosuria

Barring infections and other known diseases which alter the character of the glucose time curve the previous diet of the patient is the most important factor to control Normal individuals who have been partly depleted of their liver glycogen by a low carbohydrate diet will give a diabetic type of curve Mild diabetics on similar low carbohydrate diets may give the findings of a severe diabetic Thus to obtain a result that is the truth there should be no restriction of carbohydrate for at least three days before the test

The value of the glucose time curve is greatest in differentiating the incipient diabetic. When the venous curve leaves the diagnosis uncertain, a capillary curve will frequently settle it.

Differentiation from Severe Hypoglycemia.—Acidosis and insulin are both capable of producing coma. Their differentiation is sometimes of critical importance. *Acidosis coma* has *typical air hunger,* soft eyeballs and usually a flushed appearance with dry skin. The breath is fruity and the urine contains sugar and a strongly positive ferric chloride reaction (acetoacetic acid). In *insulin coma* the patient is pale and sweating, there is *no air hunger,* the eyeballs are not soft, twitching and convulsive movements are more common, and the urine does not contain ketone bodies. There may be sugar in the urine if the patient has not voided for more than three hours.

Prognosis

With the advent of insulin the outlook for diabetes has been completely changed. Joslin's experience shows that the average duration of diabetes has been extended from 4.9 years in the Naunyn era (1898 to 1914) to 14.1 years in the period 1944 to 1946. In similar periods the average age at death has risen from 44.5 to 64.5 years. Most diabetics today do not die of this disease but of the resulting complications. Also their general physical condition apart from diabetes plays an important part. The reliability and faithfulness of the patient to follow and the ability of the doctor to direct and carry out a modern system of treatment give the best means of assuring a normal expectation of life. The course of the disease is usually progressive but the rate of this depends upon the degree of control of the process. An increase of insulin requirement is to be looked for in the majority of patients but not necessarily so. In fact in about one third of well controlled patients the insulin requirement may decrease over the years until in some it may be removed altogether. These patients should not be considered as cured but rather that the process is latent and may return to activity during a period of physical or emotional trauma or infection. In the cases of obesity in which there is improvement with weight loss there is usually a recrudescence if the obesity returns.

In children under good control the course and life expectancy in years is even better than in adults and the complications are less serious as to life and well being until they reach the upper age decades.

At the present time the years of life expectancy at all ages is about two thirds the normal after the disease is first detected. For white persons in the United States aged 10 the expectancy for the normal is 57 more years and for the diabetic forty more; at the age of 65 it is 12 years and for the diabetic 8 years.

The principal primary causes of death in diabetics have greatly changed between 1914 and 1944 as shown below:

	1914 (%)	1944 (%)
Coma	63.8	3.1
Cardiorenal vascular	1[illegible].5	67.4
Infections	[illegible].4	7.8
Others	1[illegible].3	21.7
	100.0	100.0

The Objectives and Principles of Treatment

The objectives and principles of the treatment of diabetes mellitus are simple and straightforward. The former may be stated to be threefold, namely, the maintenance of a fairly normal blood sugar level, the maintenance of body weight within a normal range, and the prevention of acidosis and gangrene.

It must be borne in mind that diabetes is a quantitative disturbance of a particular function. In common with other similar diseases this function will deteriorate if exercised beyond its capacity over a prolonged period or if the function is not called into activity. This is particularly true in the former instance if the function is in any way embarrassed. On the contrary, it can be improved many times by putting it at comparative rest, and then by gradually making increasing demands the function may largely return toward its normal capacity. It will be outlined below how this may be accomplished in diabetes.

The occurrence of coma is in direct frequency to the severity or degree of impaired carbohydrate storage and utilization, in other words, to the control of the diabetic state as indicated by the hyperglycemia. It has been found also to be roughly parallel to the lipemia and cholesterolemia. Therefore to the principle of attempting to improve the carbohydrate metabolism there has been added the reduction of fat in the diet in the hope of avoiding this. Whether such reduction of the lipemia also helps to curtail the formation of acetoacetic and oxybutyric acids is open to question. But there seems little doubt that on a low fat and high carbohydrate diet the diabetic state is more easily controlled.

It has been suggested for many years that hypercholesteremia is a factor in the production of arteriosclerosis. There are certain experimental observations which would support this view. But it must be stated that this is not yet proved. However, even if there be a modicum of evidence in its favor it would seem in the way of wisdom to pay attention to it, as arteriosclerosis is at present the principal complication of diabetes mellitus since it is directly or indirectly the cause of most deaths and much disability. There is a close association between impaired circulation and gangrene, and the trigger to initiate the latter is very often an incidental infection of the part involved. This is most likely if the diabetic state is not under control. Therefore the meticulous care of the feet to prevent a portal of entry for infection is of the greatest importance.

Treatment.—Successful treatment of diabetes mellitus necessitates the following of a planned system. There must be complete cooperation on the part of both the doctor and the patient. Before insulin (1922) the principle of undernutrition was stressed. Subsequently, for a time, the high fat diet of Newburgh and Marsh was successfully used. Gradually from 1930 a lowering of fat and a raising of carbohydrate have been under way. It was shown that this could be done in isocaloric shifts without changing insulin requirement. Samson Geyelin and others stressed the value of the high carbohydrate diet, but not always was the total caloric content kept low and the hyperglycemia controlled. Thus in the space of a few years we have passed from a low carbohydrate to a high carbohydrate diet, from the principle

of resting to that of exercising a weakened function This is a radical change and has not yet been adopted by many students of diabetes Some have reached a halfway position, giving from 150 to 200 grams of carbohydrate per day At the Royal Victoria Hospital for the past fifteen years we have given from 200 to 300 grams of carbohydrate per day, the average being 250 grams The protein is maintained at $1\frac{1}{4}$ to 2 grams per kilogram body weight ranging from 70 to 100 grams per day while the fat is usually kept at a level of 50 grams This is not a high calorie diet In fact we average almost 200 calories less per day than when using the high fat low carbohydrate diet Values of protein 70 fat 50, and carbohydrate 250 grams give only 1777 calories

Common sense and experimental data support the principle of high carbohydrate feeding in diabetes We know that exercise improves carbohydrate tolerance It is logical to think that if we wish to strengthen a weakened physiological function, the working of it would be beneficial Using a muscle strengthens the muscle Atrophy with impaired function follows disuse Again the liver that is rich in glycogen handles glucose entering the portal circulation more efficiently By depriving a normal individual of sugar and starch for a few days the liver glycogen will be so depleted that the glucose time curve will simulate a mild diabetic Repeated glucose time curves in mild diabetics show a better utilization of carbohydrate with the second dose of glucose Critics of the low fat high carbohydrate diet have stated that fatigue of insulin production by the pancreas would develop but such has not been the case in our experience In fact tolerance progressively improves The success of the diet rests with the low calorie intake which is only possible with restricted fat

After fifteen years of experience with the low fat high carbohydrate diet as contrasted with the high fat (150 gm) low to medium carbohydrate (60 to 100 gm) diet one can make the following statements

1 The average initial insulin requirement is moderately larger but within three months it is the same or less

2 A progressive improvement of carbohydrate tolerance continues over years This was not seen with the high fat diet

3 Weight is maintained with fewer total calories (1700 to 1900) This may be explained by a greater water content of the tissues

4 The blood cholesterol averages lower from 150 to 200 mg per cent

5 The incidence of acidosis is much less

6 Infections are tolerated better due to a greater glycogen reserve

7 The tissues have a better healing power

8 There is less necessity for radical amputation in gangrene of the lower extremities

9 There is less weakness in the elderly diabetic

10 No danger from lack of vitamin A has been observed

11 The incidence of dental caries is no greater This statement is based upon the use of the diet in growing children

12 There is considerable evidence that the onset of arteriosclerosis is delayed

13 The diet is cheaper and is less upsetting to the home

14 No special foods are required

15 There is no evidence in fifteen years of any fatigue of carbohydrate tolerance

A weighed diet is to be preferred, and should be used with all children and severe diabetics Calculation in the metric system and the use of gram scales avoid carelessness, and act as a constant restraining influence upon the weakness of human nature Nevertheless excellent results can be obtained by approximated diets, especially when the diabetic state is not severe Models or the use of a standard cup a ruler and a set of standard spoons, fulfill the equipment requirements Approximated diets tend to promote guessing, and their success depends upon the mental honesty of the patient Free diets are not approved The low fat high carbohydrate diet tolerates considerable variation in carbohydrate often without appreciably affecting the blood sugar Excess of fat leads immediately to a higher insulin requirement

The diabetic tolerates more carbohydrate if he eats often The utilization of carbohydrate improves as the day progresses Accordingly small feedings of carbohydrate between meals and in the evening may be introduced when the carbohydrate intake reaches 150 grams This may be given as 10 grams in the mid morning and mid afternoon and 20 grams before retiring This leaves approximately 110 grams or more to be divided in fairly equal parts for the three main meals However as the daily quantity of carbohydrate intake approaches or passes 250 grams the between meal feedings can be increased to 20 20 and 25 grams The morning and afternoon feedings should be in the form of fruit juices while in the evening the feedings should be a soda biscuit and a glass of milk as they are more slowly absorbed Such a division of carbohydrate in the principal meals and the between meal feedings requires the least insulin

All treatment should strive for complete control of the diabetic state This implies (1) a diet sufficient in calories to maintain weight but not over weight, while in the obese under fifty a regime should be planned through diet *and exercise to reduce the weight (2) a blood sugar not exceeding 150 mg* per cent at any time in the twenty four hours, and (3) the absence of glycosuria

The Low Fat High Carbohydrate Diet

The system of building the patient up to the maintenance diet that has been found to be satisfactory follows

DAY	PROTEIN GM	FAT GM	CARBOHYDRATE GM
1	50	50	50
2	60	50	70
3	70	50	90
4	70	50	110
5	70	50	130
6	70	50	150
7	70	50	170
8	70	50	190
9	70	50	210
10	70	50	230
11	70	50	2[illegible]0

This plan requires eleven days for completion The protein is varied with the individual men doing physical work requiring 80 to 100 grams while many

TABLE X

SAMPLE MENU FOR DAY (LOW FAT HIGH CARBOHYDRATE DIET)

	WEIGHT GM	PROTEIN GM	FAT GM	CARBOHYDRATE GM
Breakfast				
Grapefruit juice	100	-	-	5
Oatmeal (cooked)	100	3	-	12
Milk	80	2	3	4
Egg	1	7	5	-
Bread (toasted)	20	2	-	10
Butter	2	-	2	-
Marmalade	10	-	-	9
		14	10	40
Forenoon				
Apple	90		-	10
Dinner				
Consommé	200	-	-	-
Liver }	80	16	4	2
Butter }	6	-	5	-
Potato	100	2	-	20
Carrots	100	1	-	9
Asparagus	100	1	-	2
Bread	50	5	1	26
Butter	5	-	4	-
Milk	40	1	2	2
Fresh peaches	200	-	-	19
		26	16	80
Afternoon				
Bread (toasted)	20	2	-	10
Butter	5	-	4	-
Jam	12		-	10
Tea with lemon	200		-	-
		2	4	20
Supper				
Tomato slices }	100	1	-	3
Peas }	100	3	-	10
Celery }	50	1	-	2
Lettuce }	50	-	-	1
Cold sliced chicken }	50	12	6	-
Bread	50	5	1	26
Milk	150	5	6	8
Butter	8	-	7	-
Banana }	70	1	-	14
Orange }	100		-	10
Sugar	6	-	-	6
		28	20	80
Evening				
Orange juice	200	-	-	20
Total values for day		70	50	250

NOTE All vegetables steamed All foods canned in syrup washed in strainer before serving

TABLE XI (A)

FOOD VALUES (COMMONER FOODS)

ARTICLE	PROTEIN PER CENT	FAT PER CENT	CARBOHYDRATE PER CENT	CALORIES PER 100 GM
VEGETABLES FRESH				
Lettuce	–	–	2	8
Cucumbers	–	–	2	8
Spinach	2	–	2	16
Asparagus	1	–	2	12
Rhubarb	–	–	2	8
Celery	1	–	3	16
Tomatoes	1	–	3	16
Brussels sprouts	1		3	16
Watercress	1		3	16
Cauliflower	2	–	4	25
Cabbage	2		[illegible]	29
Radishes	1	–	5	25
Pumpkin	1	–	6	29
String beans	2		6	33
Turnips	1		6	29
Squash	1		8	[illegible]
Beets	1		9	41
Carrots	1		9	41
Onions	1		9	41
Parsnips	1		11	49
Peas	7		15	90
Corn	3		19	90
Potato	2		20	90
Lima beans	7		22	119
Sweet potatoes	2	–	26	115
VEGETABLES CANNED				
Asparagus	1		2	[illegible]
Brussels sprouts	1		3	16
Tomatoes	1	–	3	16
String beans	1		3	16
Pumpkin	1		6	29
Peas	3		10	53
Corn	3		18	86
BERRIES AND FRUITS FRESH				
Strawberries	1	–	5	[illegible]
Grapefruit		–	5	21
Lemons	1		[illegible]	33
Watermelons	–		7	29
Blackberries	1		8	[illegible]
Cranberries		–	8	33
Peaches	–		9	37
Muskmelons		–	10	41
Raspberries	1	–	10	45
Oranges	–	–	10	41
Apples	–		11	45
Pears	–	–	11	45
Pineapples	–	–	12	49
Grapes			15	62
Cherries	–	–	17	70
Figs	1	–	17	74
Plums	1		17	74
Prunes	–		19	78
Bananas	1	–	20	86
Dates	2	–	54	234

TABLE XI (A)—CONT'D

ARTICLE	PROTEIN PER CENT	FAT PER CENT	CARBOHYDRATE PER CENT	CALORIES PER 100 GM
BERRIES AND FRUITS CANNED				
Peaches (water packed)			7	[illegible]9
Pears (water packed)	-	-	9	[illegible]7
Peaches	-	-	11	45
Blueberries	-	-	1[illegible]	[illegible]3
Pineapples	-	-	15	62
Pears	-	-	18	74
DAIRY PRODUCTS ETC				
Milk whole	3	4	[illegible]	70
Milk, condensed	9	9	11	1[illegible]
Milk skimmed	3	-	5	[illegible]3
Cream, 15 per cent fat	2	15	4	164
Cream, 20 per cent fat	[illegible]	18	4	192
Cream 40 per cent fat	1	40	3	388
Buttermilk	3	-	5	33
Butter	-	85	-	791
Olive oil	-	100	-	930
Eggs—one	7	5	-	7[illegible]
Egg white	11	-	-	45
Egg yolk	15	33	-	368
CHEESE				
American pale	[illegible]	36	-	4[illegible]3
Cottage cheese	17	2	1	186
Kraft	25	34	-	419
Beaumert	5	[illegible]8	-	374
MEATS				
Beef, cooked				
Roast	22	28	-	351
Round steak fat removed	27	8	-	185
Chopped beef fat removed	20	8	-	156
Beef canned				
Dried beef	39	5	-	206
Mutton cooked				
Leg roast	25	22	-	307
Pork				
Ham smoked lean	20	20	-	268
Bacon smoked	10	65	-	646
Bacon crisp lean	10	-	-	41
Veal cooked				
Leg roast	21	4	-	123
Chicken cooked				
Roast	22	10	-	183
Boiled	17	11	-	172
Turkey cooked (roast)	27	18	-	278
Squab one (approximate)	12	5	-	96
Liver (uncooked)	20	5	2	137
FISH FRESH				
Cod	16	-	-	66
Cod salt	27	-	-	111
Flounder	14	-	-	57
Haddock	17	-	-	70
Halibut	18	5	-	120
Mackerel	18	7	-	159
Salmon	22	13	-	211
Shad	18	9	-	158
Trout, brook	19	2	-	97
Trout lake	17	10	-	163
Blue fish	19	1	-	87
Finnan haddie	22	-	-	90
White fish	23	6	-	150

TABLE XI (A)—CONT'D

ARTICLE	PROTEIN PER CENT	FAT PER CENT	CARBOHYDRATE PER CENT	CALORIES PER 100 GM
SHELLFISH				
Clams	8	1	-	50
Lobster	16	1	-	75
Oysters	6	1	3	46
Scallops	15		3	74
FLOUR MEALS BREAD CEREALS				
Bread white	9	1	52	259
Bread graham	9	-	52	269
Wheat flour	8	1	76	354
Cornmeal	8	5	74	383
Oatmeal dry	16	7	67	405
Oatmeal (cooked weight)	3	-	12	62
Cornflakes	7	-	79	353
Rice	8	-	79	357
Rice boiled	3	-	24	111
Macaroni	13	1	74	366
Macaroni cooked	3	1	16	87
BEVERAGES				
Ginger ale	-	-	8	33
Carbonated drinks (bottled soda sarsaparilla birch beer root beer)	-	-	8	33

TABLE XI (B)

FOOD ARRANGED ACCORDING TO CARBOHYDRATE CONTENT

(For Use With Approximated Diet)

VEGETABLES (FRESH OR CANNED)

5 Per Cent		10 Per Cent	15 Per Cent	20 Per Cent
1 to 3 per cent	*3 to 5 per cent*			
Lettuce	Tomatoes	String beans	Green peas	Potatoes
Cucumbers	Cauliflower	Brussels sprouts	Parsnips	Shell beans
Spinach	Egg plant	Pumpkin	Lima beans (very young)	Baked beans
Asparagus	Cabbage	Turnips	Green corn (very young)	Lima beans
Rhubarb	Radishes	Squash		Green corn
Celery	String beans (very young)	Beets		Boiled rice
Mushrooms	Summer squash	Carrots		Boiled macaroni
		Onions		
		Green peas (very young)		

FRUIT (FRESH OR CANNED)

5 Per Cent	10 Per Cent	15 Per Cent	20 Per Cent
Fresh	*Fresh*	*Fresh*	*Fresh*
Grapefruit	Peaches	Apples	Cherries (sweet)
Strawberries	Pineapple	Pears	Figs
Watermelon	Oranges	Grapes	Plums
Canned	Lemons	Blueberries	Bananas
Peaches (water packed)	Cranberries		
Blackberries (water packed)	Muskmelons		
	Raspberries		
	Apricots		
	Blackberries		
	Gooseberries		
	Currants		
	Cherries (sour)		

women receive 70 to 80 grams In the case of inactive women 200 grams of carbohydrate will usually maintain weight High strung males not infrequently require 275 grams of carbohydrate Carbohydrate values of 300 grams have been used in cases complicated by pulmonary tuberculosis, lung abscess, or other infections As the carbohydrate reaches 150 grams the insulin requirement frequently rises, but as the higher values are given mild hypoglycemic reactions develop The nitrogen equilibrium upon the maintenance diet is satisfactory and due to the low fatty acid glucose ratio there is no danger of acidosis

In order to safeguard the growing child from vitamins A and D deficiency a cod liver oil concentrate rich in these vitamins should be given The low calcium content should also be corrected by taking one quart of whole or skimmed milk a day

The Treatment of Complications

Acidosis (Ketosis) —The treatment of diabetic ketosis is an emergency The two most important points are the relief of dehydration and the acceleration of carbohydrate oxidation by insulin

The initial insulin dose should be 50 to 150 units of crystalline zinc insulin (regular or unmodified) according to the age of the patient the severity of the acidosis the presence or not of infection and the previous insulin requirement In very urgent cases part of the initial dose may be given intravenously Subsequently at two hourly intervals three to four doses of twenty units should be given From then on for the next six hours 10 units of insulin will be needed every two hours The milder cases of acidosis will require about 150 units of insulin during the first twelve hours while the severe ones may need up to 300 units during the same interval Diabetic acidosis or coma can be treated satisfactorily by a large single dose of protamine zinc insulin supplemented by crystalline zinc insulin This procedure reduces the necessity of so many doses of crystalline insulin This is most successful and safer in the hands of those more experienced in treating diabetic coma Two hours after the first insulin 10 grams of glucose or its equivalent should be given every one to two hours until the ketosis has been relieved An intake of 50 to 100 grams of carbohydrate during the first twelve hours is desirable This intake of glucose does no harm avoids the danger of hypoglycemia and results in a greater carbohydrate oxidation Each urine specimen voided should be examined for sugar and diacetic acid If possible urine should be obtained at two hour intervals but catheterization is not justified The qualitative reaction for sugar in the urine is the best guide for insulin dosage 20 units for a red test 15 for a yellow and 10 for a yellow green test as advocated by Joslin

From the onset it is necessary to relieve dehydration An initial intravenous administration of 1000 cc of physiological saline or an equal amount of 1/6 molar sodium lactate is indicated This may be repeated if necessary As soon as possible start fluid by mouth 50 cc every fifteen minutes for five hours An intake of at least 2000 cc of fluid is essential during the first twenty four hours If vomiting or marked nausea is present a thorough

gastric lavage with warm water should be given until the washings are clear Before withdrawal of the tube [illegible]00 c c of physiological saline should be left in the stomach If vomiting continues the lavage should be repeated After any gastric lavage no food or fluid should be given by mouth for two hours The rate of output of urine is a fair guide to the amount to be given If there is a pronounced diuresis the intake should be curtailed as there may be a coincident and excessive loss of potassium (see page 8[illegible]) leading to muscular paralysis

The only indication for circulatory stimulants is in those cases showing a falling blood pressure with hemoconcentration They should be handled in the same manner as a case of shock due to water and electrolyte loss although plasma may be used This complication may occur when there has been considerable delay in initiating treatment

Alkalies should be used only when there has been loss of base as shown by a delay in the return of the plasma CO_2 capacity to normal This base loss may result from a prolonged acidosis and is especially liable to occur if a renal complication has interfered with the ability of the kidney to manufacture ammonia *The excretion of the ketone bodies as ammonium salts conserves large amounts of sodium to the body fluids* In chronic nephritis part of the acidosis may be of a retention nature and is helped by base Then the ketonuria will disappear before the plasma CO_2 capacity reaches normal If alkali is employed it must never be given intravenously but only by mouth *Doses of 4 grams of $NaHCO_3$ every three hours for two to four doses in cool water* will supply the base required but this may be even better supplied by disodium hydrogen phosphate as its secretion as dihydro sodium phosphate removes an hydrogen ion and leaves sodium to make up the deficit

There is little justification today for the death of a case of uncomplicated diabetic coma If complicated by pneumonia or acute nephritis the prognosis is grave Failure of kidney function renders the outcome serious Delay in the initiation of treatment is a common cause of failure A patient unconscious for six to twelve hours before treatment is started may recover chemically but die from circulatory failure When treating coma in the home or in the country in order to avoid the danger of hypoglycemia and to make use of large amounts of insulin permit a moderate glycosuria until the ketonuria has disappeared

Gangrene—The basis of gangrene is an impaired circulation This is mainly due to arteriosclerosis Superadded is the hyperglycemia of the uncontrolled diabetic state Something can be accomplished in preventing gangrene and this prophylactic treatment rests upon three points (1) control of the diabetic state (2) cleanliness of the feet and (3) avoidance of minor injury to the feet It is unusual to see gangrene develop with good diabetic control even if there is a marked degree of circulatory impairment Failure to keep the feet clean renders them susceptible to infections from minor abrasions Take great care in cutting corns and toe nails For detailed directions as to the care of the feet refer to Joslin s *Treatment of Diabetes* page 691 5th edition

Gangrene most commonly involves one or more toes. It may be dry or infected (moist). With it there may be an associated osteomyelitis. The treatment requires complete bed rest with slight elevation of the affected limb. A dry dressing should be applied, and all pressure of the bedclothes taken off the foot by the use of a footboard. These measures are only for protection. Heat should never be applied; in fact, it is better to keep the part cool as under these circumstances less blood is required for the nutrition of the part. The diabetic state should be strictly controlled with a diet containing at least 150 grams of carbohydrate and the necessary insulin. An estimation should be made of the efficiency of the circulation but there are no criteria that will predict with accuracy the capacity to heal. The case that fails to localize the gangrenous area after strict diabetic control has been established will require amputation. If the gangrene is moist and spreading the urgency of an amputation is much greater due to the danger of infection.

For many years the diabetic clinic in the Royal Victoria Hospital has adopted a conservative attitude in the treatment of gangrene in the diabetic. From 1925 to 1934, there were 118 cases of gangrene of the lower extremity. Of these 118 cases, 31 per cent were healed by medical means alone, 18 per cent had conservative operative procedures, usually the amputation of one or more toes, and 47 per cent suffered amputation at the knee or through the lower thigh. There was one lower leg amputation. A 47 per cent incidence of major amputations in such a series of gangrene is very low. Since the introduction of the low fat high carbohydrate diet the necessity for major amputation has dropped to 39 per cent. This policy has been pursued with slight modification. Minor reparative amputations of the toes or transtarsal operations have been become more frequent for economic reasons. The length of time consumed by the conservative medical measures sometimes offered a serious obstacle to the continuation of the treatment. Therefore these operations and even amputations below the knee at the site of election have increased in number.

As the state of the circulation is of such great importance, measures to bring about permanent improvement are often given serious consideration. These are lumbar sympathectomy and arterial denervation. Their indications rest upon the proof that vasodilatation can be produced even when all the evidences of impairment of the circulation, particularly with skin and soft tissue atrophy, are present.

The use of passive vascular exercises according to the principle of Hermann and Reid or Landis has been of great aid in a few cases of limited dry gangrene. It is contraindicated in infections. The gradual alteration of pressure (Hermann and Reid) is probably to be preferred when starting treatment, but later the sudden change of pressure (Landis) gives better results. Lately definitely better results have been obtained by intermittent venous occlusion as reported by Collens and Wilensky. Following periods of venous congestion there occurs a definite state of hyperemia as reported by Lewis and Grant in 1925. This hyperemic phase, under optimal conditions may result in a 600 per cent increase of blood flow. To it the main therapeutic benefit of this

method of treatment may be ascribed With a blood pressure cuff about the midthigh, pressures ranging from 40 mm of Hg to the diastolic level have been used, maintained for two minutes and released for two minutes and so on from two to six hours a day The lower pressures are probably indicated in the presence of infection In the author s hands this procedure in a limited number of cases of gangrene of the lower extremities in diabetics has given outstanding results An automatic apparatus for carrying out this therapy is now available (Collwil intermittent venous occlusion apparatus) As an index of the development of collateral circulation weekly measurements of the rise of the skin temperature of the foot after immersion of the arms in hot water is valuable Since the treatment of gangrene in a diabetic is a tedious affair special provision should be made for exercise by a frame over the bed As infections both tend to lead to gangrene and are serious complications antibiotics should be used as a prophylactic The most usual organism is the *Staphylococcus aureus* Therefore penicillin or streptomycin are particularly indicated (see Chapter XX)

In few departments of medicine is a closer cooperation between physician and surgeon required than in the handling of gangrene in the diabetic Consideration of age, prolonged hospitalization subsequent usefulness, and financial status have to be dealt with The danger of recurrence of gangrene is not appreciable provided diabetic control is maintained and the proper care of the feet taken

Infections —An infection in a diabetic requires prompt treatment This is especially true if the diabetic state is uncontrolled If the infection occurs in an extremity where there is impaired circulation the urgency is all the greater Treatment consists in the strict control of the diabetic state To accomplish rapid reduction of hyperglycemia give insulin every three hours and collect urines at the same intervals The insulin dosage should vary as the severity of the diabetes and the degree of infection Twenty or 30 units per dose are usually sufficient When the Benedict reaction becomes yellow halve the insulin dose Extremely severe infections require massive amounts of insulin A patient with an extensive purulent infection of a thigh received 500 units of insulin in five hours without any lowering of the blood sugar Following drainage of retained pus less insulin will be required The rapidity of spread of an infection is remarkably influenced by the diabetic control Lymphangitis may subside and cellulitis become localized

Free incision is sometimes indicated but not nearly as often as before the advent of sulfonamides and antibiotic This is particularly so with furuncles and carbuncles But before they are employed a culture of the infected area should be made to determine the infecting organism and its susceptibility to one or more of these specific agents The character of the organism will often give a direct lead but this should be confirmed In many cases the organism can be deduced fairly accurately by the character of the lesion In carbuncles it is usually the *Staphylococcus aureus* In deeper cases of cellulitis it may be the *Streptococcus hemolyticus* or some other less frequent invader while in pneumonia it is usually the pneumococcus but may be one of the other two or *H influenzae* *M tuberculosis* or a virus infection If therapy is started be

fore a culture is taken, one is always in a state of doubt as to whether the best therapeutic agent is being used At times the urgency of the condition does not warrant delay in therapy before a definite result of the culture is obtained while in others a bacteriological service is not available Under these conditions full doses of sulfadiazine penicillin streptomycin or other antibiotic is indicated It is shotgun therapy *and may turn the trick When the type of organism* and its sensitivity are definitely known more specific therapy can be employed

Before this era carbuncles were extensively incised, with a resulting large cavity for granulation and slow healing At present this is not done There may be multiple punctures of the area with silver nitrate to relieve tension or even aspiration of the necrotic fluid, with injection of the specific therapeutic agent in equivalent amounts so as not to produce tension in the tissues or a single small incision may be made for drainage

These same general rules may be applied whatever the infection may be But there are certain rules in connection with infections of the toes and feet, in particular which must be emphasized These are

1 Never apply a moist dressing if there is hyperglycemia or impaired circulation Use dry dressings only

2 Never apply or bathe the feet in strong antiseptic solutions (iodine lysol etc)

3 Control the hyperglycemia before extensive incision or drainage

4 If hyperglycemia has been controlled and there is good palpable pulsation in the dorsalis pedis vessel, interrupted moist dressings without rubber protective can be safely used

Hyperthyroidism—Hyperglycemia and glycosuria occur frequently in cases of toxic goiter *The degree of glycosuria is mild, and the fasting blood* sugar is normal This hyperglycemia is dependent upon faulty or impaired glycogen formation and storage by the liver and disappears after the hyperthyroidism has been controlled One must not confuse this type of glycosuria with the true diabetic state associated with toxic goiter Both conditions must be recognized and treated Neither of these conditions is rare and the chances of their occurring in the same individual are not remote The real danger is the acceptance of the glycosuria as being a simple manifestation of the hyperthyroidism and not due to a truly diabetic state Coma never occurs in hyperthyroidism except in the extreme stages of a thyrotoxic crisis and is then due to circulatory failure or/and hyperpyrexia Indications of acidosis such as acetonuria are not present unless due to starvation while the CO_2 combining power of the plasma is within normal limits In fact there may be hyperpnea in order to satisfy the excessive oxidation requirements and the CO_2 combining power may be elevated

This combination is well demonstrated by a middle aged woman in a state of unconsciousness from a diabetic ketosis with a high blood sugar and glycosuria Her pulse rate was 160 per minute the skin was warm and moist and there was slight fullness with increased vascularity of the thyroid gland To suitable treatment for the acidosis 90 minims of Lugol s solution per day were given In twenty four hours her pulse dropped by crisis to 90 per minute, the acidosis had been relieved, and one week later a bilateral thyroidectomy was

done without the pulse rate rising above 100 per minute Today after many years her basal metabolic rate is normal and the diabetic state is under good control by diet and 40 units of insulin

The Use of Insulin

Insulin is an aid, not a cure, in the treatment of diabetes Its use is indicated when a diet suitable for the needs of the patient will not alone control the diabetic state Insulin is practically inactive by mouth, so has to be given subcutaneously *In emergencies it may be used intravenously*

There are three main types of insulin being used in North America today namely crystalline zinc (regular unmodified) protamine zinc and globin Commercially these insulins are prepared in 40 and 80 units per c c strengths It is good practice to use a strength that will avoid a volume of fluid larger than 1 c c These insulins have different periods of action Crystalline zinc has its peak action in 3 to 4 hours with a total 12 hours action Protamine zinc has a 24 to 28 hour action and at no one time is there any large amount of free insulin liberated from the mixture Globin insulin has an intermediate position its duration of action being from 16 to 20 hours Crystalline zinc and globin insulin should be given 30 minutes before meals so as to balance the hyperglycemic effect of the meal Protamine zinc insulin is usually given before breakfast but there is no advantage in waiting 30 minutes after its administration before eating

In the course of treating every diabetic a decision has to be made—does or does not the patient need insulin? If he does the next decision is the type of insulin to be used For the new untreated adult diabetic a satisfactory scheme to follow is to start the patient on a small dose (12 to 16 units) of protamine zinc insulin before breakfast Build up this dose progressively by 4 unit increments as you are increasing the diet until the fasting urine is free from glycosuria Then check the fasting blood sugar which should be normal With one dose of protamine zinc insulin a day taken before breakfast the fasting blood sugar is the lowest in the 24 hours and the highest blood sugar is usually found one hour after the noon meal After the fasting blood sugar is normal investigate the urine and blood sugar one hour after the noon meal If there is no glycosuria and the blood sugar does not exceed 150 mg per cent you have good control of your diabetic with one dose of protamine zinc insulin This is only possible in the milder group of diabetics that need insulin

When the diabetic state is more severe the blood sugar one hour after the noon meal will be well above 150 mg per cent and then it is necessary to supplement the protamine zinc with crystalline zinc insulin The latter dose initially a small one (8 to 12 units) should be given 30 minutes before breakfast followed by the protamine zinc dose The crystalline zinc dose is increased by increments of 4 units until the blood sugar 4 hours after its administration is normal Then study the level of the blood sugar one hour after the noon meal If it does not exceed 150 mg per cent you have good control with *one* dose of protamine zinc and one dose of crystalline zinc insulin both before breakfast If the blood sugar one hour after the noon meal is still high it will be necessary to start a crystalline zinc dose 30 minutes before

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hours after its administration although some patients may develop hypoglycemia in the late afternoon from a before breakfast crystalline zinc dose. Globin insulin given before breakfast will usually have its low point in the late afternoon although hypoglycemia may occur in the forenoon.

An insulin reaction not explained by some irregularity in insulin dosage or food eaten, may be due to (1) an unusual amount of exercise, (2) delayed absorption of food or (3) an improvement of carbohydrate tolerance (greater output of endogenous insulin). The effect of exercise upon insulin requirement is so striking that Joslin considers that it stands next to diet and insulin in the treatment of diabetes. Delayed digestion and absorption of food occurs in patients whose general vitality is low. These reactions may be severe and dangerous.

Patients should be taught to be suspicious of any uncomfortable sensations occurring at the times when insulin reactions might occur. By paying attention to mild symptoms and treating them serious symptoms will be avoided. The patient who disregards mild symptoms, on subsequent days will develop severe ones. All patients starting insulin should be intentionally given a mild reaction so that they will recognize it in the future and experience the result of treatment. This is of special importance because recurring hypoglycemia in the same patient tends to develop similar symptoms.

Mild and moderate hypoglycemia from crystalline zinc and globin insulin is satisfactorily treated by 5 grams of glucose or its equivalent every ten minutes by mouth until all symptoms are abolished. If unconsciousness has developed 10 grams of glucose intravenously will awake up the patient to be followed by 5 grams by mouth as necessary. Glucose by rectum in a larger dosage ([illegible] grams) is effective. Glucose prepared in 5 gram powders is convenient but orange juice corn syrup or glucose candies will do as well. To meet an emergency 1 c c of 1 in 1 000 solution of adrenalin chloride may be given to an adult. This will cause a temporary rise in the blood sugar provided there is glycogen in the liver. Adrenalin when used must always be followed by glucose otherwise the patient will revert into a more severe hypoglycemic state. To a child one half of the above dose of adrenalin may be given. Following an insulin reaction the diet should remain unchanged but the insulin must be decreased. Hypoglycemia from protamine zinc insulin should first be treated with 5 Gm of glucose or its equivalent and in 10 minutes 100 c c of milk ([illegible] glass) and a soda biscuit. Protamine zinc reactions tend to recur thus the necessity for giving a more slowly absorbing form of carbohydrate. In an adult the insulin responsible should be reduced by 4 units in a child by 2 units. All insulin reactions should be systematically treated and indiscriminate eating discouraged. Every patient taking insulin should always carry with him the means of treating a reaction as well as an identification card stating that he has diabetes is taking insulin and the dose being taken. Such a precaution may be life saving.

If insulin is injected too frequently into the same area the subcutaneous tissues become nodular from delayed absorption. Accordingly the arms and

the noon meal Thus the milder cases that need insulin will be controlled by one dose of protamine zinc while the severer cases may require a dose of protamine zinc before breakfast and a dose of crystalline zinc before breakfast before dinner, and even before the night meal

When crystalline zinc insulin is used alone a single dose before breakfast is rarely satisfactory It is usually necessary to give a dose before breakfast and again before supper These doses should be equal in unitage if possible In the severer cases a noon dose will be necessary this to be smaller than the morning and night doses Most diabetics can be nicely controlled by day with crystalline zinc insulin but in the severer cases the blood sugar rises after midnight to reach its highest level before breakfast

Since globin insulin is an intermediate insulin it can be used to handle the day period in many cases while protamine zinc is employed to cover the night hours Globin insulin given before breakfast can often be substituted for 2 doses of crystalline zinc insulin with good results In the milder cases one dose of globin insulin alone before breakfast may carry the patient through to a satisfactory blood sugar before breakfast the next morning

The efficiency of insulin is in part dependent upon the management of the diet It is our plan to introduce between meal feedings when the total carbohydrate of the diet reaches 150 grams These consist of 10 grams of carbohydrate in the forenoon 10 grams in the afternoon and 15 grams in the evening After the total between meal values have been subtracted from the total values of the day the balance is divided equally between the three main meals The between meal feedings may be varied considerably to meet the individual case When using globin insulin better control is established with a smaller breakfast so the main meals are one fifth two fifths and two fifths of the remaining values

Complications—The main complication following insulin administration is hypoglycemia This is due to great lowering of the blood sugar In adults mild symptoms nervousness tremor and palpitation appear when the blood sugar falls to 50 to 60 mg per cent As the value drops to 40 to 50 mg per cent, sweating is constant and is the forerunner of the more serious signs Convulsions, coma and death occur only with extremely low blood sugar values 20 mg per cent or less Children can have much lower blood sugar values without symptoms than adults Values of 30 mg per cent are not unusual The rate of drop of the blood sugar especially in elderly arteriosclerotic patients influences the level at which symptoms appear With a rapidly dropping blood sugar in such cases the author has seen moderate symptoms at 100 mg per cent Children also complain of double vision adults may simulate alcoholic hilarity while rarely patients may become unconscious without warning Headache as a symptom of hypoglycemia from protamine zinc insulin is not uncommon Rarely is it seen with crystalline zinc insulin

Insulin reactions must be coordinated with the kind of insulin that is being used Protamine zinc reactions occur after midnight usually from 3 to 7 A M The earlier in the night that it occurs the greater is the disproportion between dosage and requirement Crystalline zinc reactions occur 3 to 4

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Since globin insulin is an intermediate insulin it can be used to handle the day period in many cases while protamine zinc is employed to cover the night hours. Globin insulin given before breakfast can often be substituted for 2 doses of crystalline zinc insulin with good results. In the milder cases one dose of globin insulin alone before breakfast may carry the patient through to a satisfactory blood sugar before breakfast the next morning.

The efficiency of insulin is in part dependent upon the management of the diet. It is our plan to introduce between meal feedings when the total carbohydrate of the diet reaches 150 grams. These consist of 10 grams of carbohydrate in the forenoon, 10 grams in the afternoon and 15 grams in the evening. After the total between meal values have been subtracted from the total values of the day, the balance is divided equally between the three main meals. The between meal feedings may be varied considerably to meet the individual case. When using globin insulin better control is established with a smaller breakfast so the main meals are one fifth, two fifths and two fifths of the remaining values.

Complications.—The main complication following insulin administration is hypoglycemia. This is due to great lowering of the blood sugar. In adults mild symptoms, nervousness, tremor, and palpitation appear when the blood sugar falls to 50 to 60 mg. per cent. As the value drops to 40 to 50 mg. per cent, sweating is constant and is the forerunner of the more serious signs. Convulsions, coma and death occur only with extremely low blood sugar values, 20 mg. per cent or less. Children can have much lower blood sugar values without symptoms than adults. Values of 30 mg. per cent are not unusual. The rate of drop of the blood sugar, especially in elderly arteriosclerotic patients, influences the level at which symptoms appear. With a rapidly dropping blood sugar in such cases the author has seen moderate symptoms at 100 mg. per cent. Children also complain of double vision; adults may simulate alcoholic hilarity, while rarely patients may become unconscious without warning. Headache is a symptom of hypoglycemia from protamine zinc insulin is not uncommon. Rarely is it seen with crystalline zinc insulin.

Insulin reactions must be coordinated with the kind of insulin that is being used. Protamine zinc reactions occur after midnight usually from 5 to 7 A.M. The earlier in the night that it occurs the greater is the disproportion between dosage and requirement. Crystalline zinc reactions occur 3 to 4

hours after its administration although some patients may develop hypoglycemia in the late afternoon from a before breakfast crystalline zinc dose. Globin insulin given before breakfast will usually have its low point in the late afternoon although hypoglycemia may occur in the forenoon.

An *insulin reaction*, not explained by some irregularity in insulin dosage or food eaten, may be due to (1) an unusual amount of exercise, (2) delayed absorption of food or (3) an improvement of carbohydrate tolerance (greater output of endogenous insulin). The effect of exercise upon insulin requirement is so striking that Joslin considers that it stands next to diet and *insulin in the treatment of diabetes*. *Delayed digestion and absorption of food* occurs in patients whose general vitality is low. These reactions may be severe and dangerous.

Patients should be taught to be suspicious of any uncomfortable sensations occurring at the times when insulin reactions might occur. By paying attention to mild symptoms and treating them serious symptoms will be avoided. The patient who disregards mild symptoms on subsequent days will *develop severe ones*. *All patients starting insulin should be intentionally given* a mild reaction so that they will recognize it in the future and experience the result of treatment. This is of special importance because recurring hypoglycemia in the same patient tends to develop similar symptoms.

Mild and moderate hypoglycemia from crystalline zinc and globin insulin is satisfactorily treated by 5 grams of glucose or its *equivalent* every ten minutes by mouth until all symptoms are abolished. If unconsciousness has developed 10 grams of glucose intravenously will wake up the patient to be followed by 5 grams by mouth as necessary. Glucose by rectum in a larger dosage (15 grams) is effective. Glucose prepared in 5 gram powders is convenient but orange juice corn syrup or glucose candies will do as well. To meet an emergency 1 c c of 1 in 1 000 solution of adrenalin chloride may be given to an adult. This will cause a temporary rise in the blood sugar provided there is glycogen in the liver. Adrenalin when used must always be followed by glucose otherwise the patient will revert into a more severe hypoglycemic state. To a child one half of the above dose of adrenalin may be given. Following an insulin reaction the diet should remain unchanged but the insulin must be decreased. Hypoglycemia from protamine zinc insulin should first be treated with 5 Gm of glucose or its equivalent and in 10 minutes 100 c c of milk (½ glass) and a soda biscuit. Protamine zinc *reactions tend to recur* thus the necessity for giving a more slowly absorbing form of carbohydrate. In an adult the insulin responsible should be reduced by 4 units in a child by 2 units. All insulin reactions should be systematically treated and indiscriminate eating discouraged. Every patient taking insulin should always carry with him the means of treating a reaction as well as an *identification card stating that he has diabetes* is taking insulin and the dose being taken. Such a precaution may be life saving.

If insulin is injected too frequently into the same area the subcutaneous tissues become nodular from delayed absorption. Accordingly the arms and

legs should be used in rotation, avoiding any thickened areas Rarely at the site of repeated insulin injections a complete atrophy of the subcutaneous fat takes place leaving a groove When such happens the area should be avoided as a site of further injections Daily massage will gradually restore the normal contour of the part

In the early days of insulin a great deal of trouble was experienced with allergic reactions They varied from a local erythema with induration at the site of injection to a systemic urticaria with extreme facial edema The protein content of the fluid was usually the cause, but cases of sensitivity to the preservative used, or the reaction of the fluid have been seen Today individuals sensitive to insulin are observed infrequently If the sensitization is mild all evidence of it usually disappears after a few weeks Changing to a more concentrated solution is sometimes effective Pork or sheep insulin should be tried when beef insulin is not tolerated The use of the antihistamine drugs is helpful

About 30 per cent of patients who start insulin have been able to discontinue it within two years This should dispel the idea widespread among the laity that once insulin always insulin

The Use of Drugs

Exclusive of insulin there are no drugs that have any curative effect in the treatment of diabetes Many preparations, patented or otherwise, are advertised as being effective by mouth but they are useless Other drugs should be used to alleviate symptoms as in nondiabetics

Exercise and Carbohydrate Tolerance

Before insulin the value of exercise in lowering the blood sugar of a mild diabetic was well appreciated Since exogenous insulin can supply the endogenous deficiency, exercise is applicable to all diabetics today provided their general condition does not contraindicate it The blood sugar lowering from exercise is most marked in the child and necessitates extra carbohydrate before strenuous games and gym" classes Even during hospital periods less insulin is required if regular exercise can be arranged for The bed ridden diabetic with gangrene of the lower extremity should have daily exercise of the arms So great is the improvement from exercise that a precautionary lowering of the insulin dosage upon discharge from the hospital is advisable

The Diabetic Child

The diabetic child is a growing organism and therefore requires special care The diet should be readjusted at yearly intervals Height and weight should be followed and overweight must be rigorously avoided During the period of puberty special care is necessary

The nutrition of the diabetic child should be based upon actual height Diets for diabetic children should be calculated upon theoretical weight for actual height Since some of these children are considerably overheight for their age a compromise in the values of the diet has to be made

A dietetic plan for children from birth to 20 years of age that has been found to be fairly satisfactory is as follows

AGE PERIOD	TOTAL CALORIES PER KILO	PROTEIN GM PER KILO	FAT GM	C H O GM
0 to 5 years	100 to 80	5	[illegible]0 to 60	[illegible]
6 to 10 years	80 to 60	4	60 to [illegible]0	
11 to 15 years	60 to 40	3	[illegible]0 to 80	
16 to 20 years	40 to 30	[illegible]	60 to [illegible]0	

The above scheme provides the maintenance values The child should be built up to these values by graded stages from a lower diet When actual height is normal for age the scheme requires very little modification Children should have three main meals with forenoon afternoon and evening feedings After subtraction of the between-meal feedings from the total values the remaining values should be divided equally between the three meals All diabetic children's diets should be calculated and weighed in the metric system

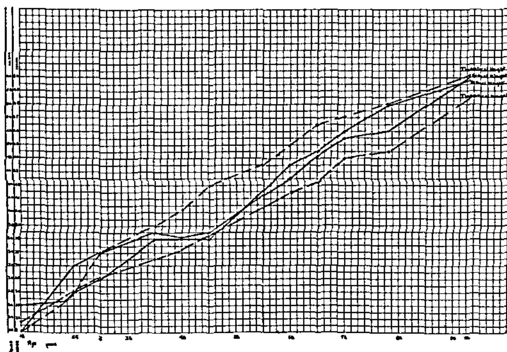


Chart XXVII—Height and weight curves of a diabetic child treated with insulin as compared with the average normal Onset of diabetes at eighteen months

In addition to the calories care should be taken to supply a normal amount of calcium (milk) Vitamin supplements are essential

During the first year of diabetic life in a child there may be very little tendency for the blood sugar to rise in the night so *crystalline zinc insulin* two doses a day can be used and good control maintained This is helpful for the mother in that insulin reactions then occur by day and are more easily handled Shortly however fasting hyperglycemia will appear in most cases,

and the use of protamine zinc and crystalline zinc insulin are imperative. Some cases are being well controlled by combinations of protamine zinc and globin insulin.

The future of these children depends upon their control. The incidence of complications is much higher in the poorly controlled cases.

Diabetic children respond readily to exercise by a lowering of the blood sugar. "Gym" classes should be preceded by five or ten grams of extra carbohydrate. Contact with open cases of tuberculosis should be strictly avoided.

Diabetes and Pregnancy

In the preinsulin era the incidence of fertility of diabetic women was low, varying from 2 to 6 per cent in different clinics. The cause of this low fertility was not exactly known, but most probably it was related to the degree of undernutrition as well as the partial failure of pituitary function (gonadotrophic factor) resulting in infantile development of the uterus and amenorrhea.

With the insulin era the pregnancy rate has increased to about 35 per cent. Also large numbers of diabetic children have now reached maturity and have borne children. The pregnancy risk for the mother in a diabetic patient is not much greater than in a nondiabetic woman. White has reported a maternal survival rate of 99.6 per cent in a series of 271 consecutive diabetic pregnancies. This figure is even better than the accepted 0.6 per cent for nondiabetic women. Such a satisfactory survival rate has not been attained for the fetus, and until recent years the advent of insulin did not greatly lower the fetal mortality. More recently, with careful correction of the imbalance of sex hormones, White has been able to raise the fetal survival rate to 90 per cent. This is a triumph for modern medicine.

The main abnormalities that contribute to the high fetal mortality are vascular disease, hypo-ovarianism and uterine irritability in the mother. Imbalance of the sex hormones and water retention leading to hydramnios and fetal edema are also of major importance. Finally, oversized infants and atelectasis contribute to the picture. Of all the above abnormalities the imbalance of the sex hormones is the most important.

An imbalance of the sex hormones is present in about 50 per cent of diabetic pregnancies and manifests itself by a low pregnandiol excretion, a low serum level of estrin and a high serum level of chorionic gonadotrophin.

The dietetic management of the mother does not need to be changed with the onset of pregnancy. The low fat high carbohydrate diet has been found satisfactory. The protein intake should be at least 1¼ to 1½ grams per kilogram of body weight. Extra calcium and vitamin intake is essential. The regular insulin requirement does not change appreciably until the start of the third trimester when it tends to increase. A successful outcome depends a great deal upon the strict control of the diabetic state. Those cases that show hormonal imbalance as determined by high serum prolan (chorionic gonadotrophin), and low pregnandiol excretion, and if they show associated signs of toxemia such as increasing blood pressure, albuminuria and edema, had best be treated, according to White, with progesterone and estrogen.

In the main the best type of delivery is by cesarean section Only those cases that are mild have borne children previously and have shown no sign of toxicity should be allowed to deliver themselves Primiparous mothers those who have lost a previous pregnancy and those who have experienced toxemia or hormonal imbalance should be delivered by cesarean section toward the end of the thirty seventh week

After delivery the mother is best handled with crystalline zinc insulin for a few days If there has been an increasing insulin requirement prior to delivery it will be necessary to reduce the dosage rather rapidly to the patient s basic level

The blood sugar of the infant is usually normal at birth but tends to be unstable and may fall during the first four hours to mild hypoglycemic levels Feedings of 5 grams of glucose in water every two hours from birth for 48 hours will prevent hypoglycemia

Surgical Operations Upon Diabetics

Excluding surgical interference for complications referable to the diabetic state (infections and gangrene with arteriosclerosis of the lower extremity) there is no surgical operation today that cannot be carried out upon the controlled diabetic with practically the same risk that is incurred with the nondiabetic the physical state in other respects being equal In fact our diabetics after major operations (cholecystectomies appendectomies, thyroidectomies etc) suffer less postoperative vomiting and discomfort than a comparable group of nondiabetics *This is due to a greater attention to detail* and more care as to the maintenance of a proper glycogen reserve both preoperatively and postoperatively *The tissues of the controlled diabetic heal* at a normal rate provided there is no impairment of circulation

The preoperative preparation of the diabetic should assure an adequate glycogen reserve freedom from acidosis and dehydration and a blood sugar below 150 mg per cent If time is available the carbohydrate intake should be from 150 to 200 grams per day for two days preoperatively Sufficient insulin should be given to assure utilization On the day of the operation and for a few days postoperatively we prefer to use crystalline zinc insulin because of the shorter duration of action in a period of uncertain food intake On the morning of the operation breakfast is omitted and a small dose of crystalline zinc insulin is given Postoperatively an intravenous injection of 1000 c c of 5 per cent glucose and saline along with 16 to 20 units of crystalline zinc insulin is given This may be repeated 6 hours later using 5 per cent glucose in water Subsequently for one to two days 10 to 15 grams of carbohydrate at two to three hour intervals are given and covered with insulin *With the taking of soft food four light meals containing the total* values of protein 50 grams fat 50 grams and carbohydrate 100 grams are tried *Insulin is given before the first second and fourth meals As recovery* progresses these values are increased in protein and carbohydrate and a three *meal regime is established*

With the aid of insulin the kind of anesthetic is of less importance than formerly Chloroform and protracted ether administration should be strictly

avoided Nitrous oxide and oxygen, ethylene, spinal, or local anesthesia, are to be preferred Ether, if used, should be removed from the tissues by rebreathing or by breathing 5 per cent CO_2 in oxygen This avoids nausea, vomiting, and inability to take fluids

The Instruction of the Diabetic

The success of all diabetic treatment depends upon an intelligent cooperation on the part of the patient To gain such cooperation it is imperative that certain rudimentary knowledge of the disease and its care be given This is best accomplished by organized classes of instruction as found in diabetic clinics

The diabetic should know as a minimum

1 A brief story of the nature of his disease and the importance of diet in its treatment, the commoner complications and how they can be avoided (coma, gangrene, infections)

2 The preparation of the diet, weighed or approximated If weighed, the calculation of the diet in the metric system

3 The administration of insulin the recognition of hypoglycemia and its treatment

4 Examination of the urine for sugar (Benedict's or Clinitest) and for diacetic acid (ferric chloride)

5 What to do as to diet and insulin if glycosuria or hypoglycemia appear

6 Care of the feet (especially applicable to patients over fifty years of age)

During the period of instruction Joslin's *Diabetic Manual* is a valuable source of information for the patient From the onset a notebook should be kept which in time will be helpful for reference

The New Disease

With the prolongation of life referable to insulin, the medical profession is today confronted with a new disease What is the complete future of the diabetic child is still unknown Those of us who have seen these children grow to maturity marry, bear children of their own, and take their part in the modern world, realize keenly the tremendous progress in the treatment of diabetes mellitus

HYPERINSULINISM

Hyperinsulinism is the syndrome of spontaneous intermittent or continuous loss of consciousness with or without convulsions, from excessive production of insulin by the pancreatic islands of Langerhans The usual symptoms of hypoglycemia occur namely nervousness, tremor, perspiration, and palpitation, progressing as the blood sugar falls and finally convulsions loss of consciousness and even death

This condition has been recognized only in recent years as the understanding of the insulin reaction has become more general The pancreatic

lesion usually found has been either an hypertrophy of the island tissues, an adenoma, or a carcinomatous growth Rarely has the lesion been extrapancreatic as in Anderson's fatal case due to an adrenal tumor Many instances are on record where no specific lesion could be found at operation or autopsy to account for the spontaneous hypoglycemia Surgical removal of a pancreatic tumor has effected a cure in a limited number of cases *

Symptoms —The symptoms of hyperinsulinism are dependent upon the degree of lowering of the blood sugar and its duration Most adults start to develop nervousness tremor and palpitation with a blood sugar of 60 mg per cent, while children may not show any symptoms until the value has reached 30 mg per cent Due to their late onset in children, the symptoms progress more rapidly loss of consciousness with convulsions occurring with little warning

Diagnosis —An exact diagnosis depends upon coordinating the attacks with a blood sugar low enough to account for them To do this, those cases having intermittent attacks will have to be kept under supervision Fasting or strenuous physical exercise may be helpful to initiate an attack in doubtful cases The therapeutic effect of 5 or 10 grams of glucose administered either by mouth or intravenously is also of great aid Marked improvement should be prompt but temporary The use of the glucose time curve is of diagnostic value It should be carried on for six hours A hypoglycemic blood sugar level after the third hour is significant

The following criteria are generally considered essential for the diagnosis of organic hyperinsulinism

1 Fasting blood sugars below 60 mg per cent
2 Immediate relief of proved hypoglycemia with intravenous glucose
3 A characteristic glucose tolerance test
4 A capacity above the normal to remove glucose from the blood stream when glucose is administered intravenously at a constant rate

Hyperinsulinism is most frequently mistaken for epilepsy or hysteria but the character of the attack coordinated with the clinical picture and the blood sugar should make differentiation easy

Treatment —Medical treatment in severe cases is unsatisfactory The necessity for almost continuous carbohydrate administration makes it impracticable But in moderate cases particularly those in which no anatomical explanation is found small and evenly distributed carbohydrate meals are helpful Some patients maintain a better blood sugar on high protein and high fat meals rather than upon high carbohydrate feedings High carbohydrate meals tend to be followed by marked hypoglycemia Epinephrin (0 5 to 1 c c) helps to overcome acute attacks while nembutal and amytal have a beneficial effect Surgical exploration in clear cut cases is justified and recommended Removal of an adenoma has resulted in a cure Partial removal of an abnormal pancreas has led to some improvement †

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* The senior author has seen four cases which immediately followed so called attacks of influenza but eventually developed signs of Parkinson's disease

† In one case which remained under observation for many months ergoklonin (Wyeth) gave decided relief of symptoms and prevented the pronounced fall of blood sugar after a carbohydrate meal

RENAL GLYCOSURIA

(Renal Diabetes)

Renal glycosuria is a condition where sugar (glucose) is passed in the urine at the time when the blood sugar is normal This is due to a lowered glucose threshold in the kidney The condition *per se* results in no symptoms, there is no impairment of health, and there is no justification for dietetic restriction Accordingly in true cases there is no interference with the normal expectation of life

There are three main types of renal glycosuria, (1) hereditary or idiopathic, (2) cyclic, and (3) when associated with pregnancy The *idiopathic type* is a clear cut entity, unchanging when observed over many years These individuals have a lowered glucose threshold in the kidneys so that they constantly excrete small amounts of dextrose Many individuals of the same family may be affected, and the condition persists for life The *cyclic type* is a recurring mild glycosuria in digestive periods when the blood sugar is below the normal threshold There is no glycosuria in the fasting state due to the threshold being only slightly lowered This diagnosis in the past has been made largely through the study of venous blood, which offers a chance for error A synchronous determination of the arterial or capillary blood sugar after immersion of the arm in hot water has shown that when this cyclic glycosuria occurs the arterial sugar value is frequently above the normal threshold level of 170 mg per cent Thus many of these cases are really mild diabetics *Renal glycosuria associated with pregnancy* is not uncommon In pregnancy there is a temporary lowering of the renal threshold for glucose so that the findings may be identical with the hereditary type After delivery the threshold returns to its normal level, the glycosuria ceasing only to recur with subsequent pregnancies

Pathogenesis—With Richard's studies upon the kidney function, the mechanism of the glucose threshold in the kidney has been explained The glomerular fluid would appear to be a true filtrate through Bowman s capsule Its concentration in glucose is the same as that of the blood in the afferent artery coming to the glomerulus As the glomerular fluid passes downward through the convoluted tubules glucose is rapidly absorbed Thus glucose absorption is a specific function of the cells lining the proximal convoluted tubules These cells may fail to reabsorb the glucose completely, with the result that a small amount remains in the tubular fluid and reaches the pelvis of the kidney in the urine To date no histological alteration has been noted in the tubular cells of idiopathic cases of renal glycosuria However, renal glycosuria is frequently observed in diseases where there is tubular cell degeneration (see Fig 321)

Diagnosis—The exact diagnosis of renal glycosuria necessitates a careful coordination of the blood and urine sugar levels in synchronous periods Care must be taken to consider the glucose threshold in the kidney in terms of arterial blood or its equivalent Only in the fasting state are the venous and arterial values identical In all digestive periods the arterial sugar is

somewhat higher than the venous due to removal of glucose from the capillary blood The attempt to judge renal glucose thresholds from the venous blood in the digestive state invalidates a large amount of the published data

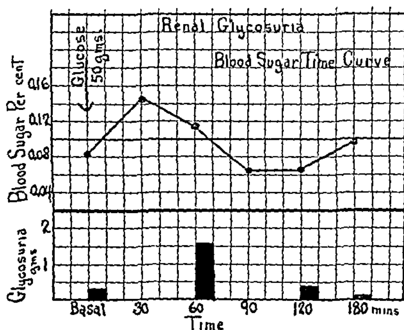


Chart XXVIII —Glucose time curve in a case of renal glycosuria

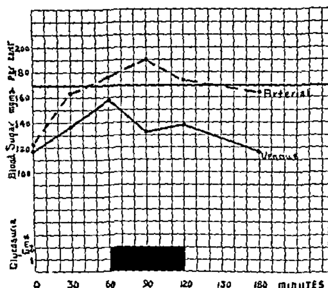


Chart XXIX —A threshold determination in renal glycosuria obtained by comparing venous and capillary blood sugar curves Note parallelism of the level of the capillary blood sugar and glycosuria

True renal glycosuria is present almost continuously and the threshold can frequently be determined by examination of the urine and venous blood hourly in the fasting state The level of the blood sugar at which the

glycosuria ceases is the threshold This may be 100 mg per cent or even lower The writer has seen cases with thresholds of 70 mg per cent, so low that glycosuria continued even when the fasting state was prolonged from 8 A M to 2 P M The twenty four hour glucose excretion usually does not exceed 10 grams, and is only slightly influenced by the carbohydrate intake The blood sugar (venous) *curve after the administration of 100 grams of* glucose by mouth should be normal with the maximum value in thirty minutes, and not exceeding 150 mg per cent The return to the fasting level should follow in one and a half to two hours, following which there should be a temporary period of mild hypoglycemia Frequently the glucose time curve indicates a tolerance greater than the average normal In the case of the renal glycosuria of pregnancy the glucose time curve may show delayed glycogen storage, probably due to a deficiency of liver glycogen through increased demand

Uncomplicated cases of renal glycosuria have no symptomatology, and observation over several years shows no change in the threshold or glycosuria No progression into diabetes mellitus has been observed In the diagnosis of all nondiabetic glycosurias the exact chemical nature of the reducing substance present should be determined In renal glycosuria it is always dextrose

A more complete study of these cases would include evidence obtained by respiratory studies, that the oxidation rate of carbohydrate by the tissues was normal

One must remember that renal glycosuria and diabetes mellitus can occur in the same case Only after the hyperglycemia has been controlled does the persistent slight glycosuria point to a lowered renal threshold Renal glycosuria is frequently seen in cases of degenerative tubular nephritis (nephrosis) where it may persist until death It has also been observed in temporary degenerative lesions of the kidney

Treatment—The typical case of renal glycosuria needs no special treatment Dietetic restriction is definitely contraindicated, and when employed through misdiagnosis frequently results in marked loss of weight However at yearly intervals for several years the patient should be reexamined both as a protection to himself and to the doctor

The cyclic type of renal glycosuria should be watched more carefully and checks carried out upon the arterial or capillary bloods at three month intervals Many of these cases will be found to be mild diabetics

Since the renal glycosuria of pregnancy is only temporary and presents all the features of the true renal glycosuria no special treatment is necessary

ACID BASE BALANCE

The animal organism will not tolerate changes of its internal environment and exerts great adaptability in circumventing them and maintaining an exquisite equilibrium The one most jealously guarded is the hydrogen ion concentration which is maintained by the acid base balance It is true that the constitution of the blood is not constant in all its parts nor is it an absolute index at all times of the hydrogen ion concentration of the cells To some

extent it can be used as an index or a reflection of the cellular condition in this regard The venous blood contains more carbon dioxide and lactic acid than does the arterial blood This would suggest that the former would be more acid than the latter but when it is appreciated that oxyhemoglobin is more acid than the reduced hemoglobin it will be obvious that there is a fairly steady balance indicated by the venous blood The principal means for maintaining the constancy of the hydrogen ion equilibrium at short notice is by the cellular dissociation of carbon dioxide thus changing the ratio of $\frac{H\ CO_3}{B\ H\ CO_3}$ It has been stated that the blood may act as an indicator of the condition in the cells This is hardly true but rather it reflects the tendency of the hydrogen ion concentration of the internal environment to be modified in one or other direction It is often stated that the pH of the blood has either risen or fallen a certain degree It is, therefore inferred that the pH of the cells has likewise changed It is doubtful whether any of our modern physical instruments are delicate and accurate enough to register the changes in pH which a cell could tolerate It has been difficult to determine the range over which the hydrogen ion concentration of a mammalian cell can be modified and still maintain its functional activity

There is a small group of cells in the midbrain called the respiratory center, which has a functional rather than a strictly anatomical entity It has been postulated that this center is so sensitive to changes in pH that it responds to changes which cannot be detected by our best physical methods I do not think that it is taking too much for granted if we presume that all cells are equally sensitive to changes in their hydrogen ion concentration, but the cells of the respiratory center are more articulate in this regard The $\frac{H\ CO_3}{B\ H\ CO_3}$ ratio can be looked upon as the fine adjustment in the maintenance of this imperative equilibrium If for any reason the hydrogen ion concentration of the tissues in general tends to increase to the minutest degree the respiratory center responds by increasing the pulmonary ventilation This reduces the CO_2 in the alveolar air, which in turn increases its diffusion outward and lowers its concentration in the arterial blood which affects the ratio in the cells and so the equilibrium is maintained On the contrary if the hydrogen ion concentration declines the stimulation to the respiratory center is depressed and pulmonary ventilation is reduced thus allowing CO_2 of the alveolar air to rise and in turn affect the ratio in an opposite direction by the retention of carbon dioxide

Carbon dioxide on account of its great solubility its weak acid character and its easy dissociation is an ideal substance for the maintenance of this delicate equilibrium Through the vicissitudes of the ordinary daily life of an average normal individual changes in the alveolar air and blood can be detected as for instance during the cycle of digestion when there is a large outpouring of acid ions in the gastric juice the CO_2 combining power of the blood and its percentage in the alveolar air rises but a short time later when the relatively alkaline pancreatic and biliary excretions take place the

opposite occurs This can also be repeated by the ingestion of relatively large amounts of alkaline or acid substances

The range over which carbon dioxide elimination or retention can exert its influence on the constancy of the cellular pH is a comparatively narrow one, and if the body were solely dependent upon it, we should be in a constant state of hyperpnea or apnea The lungs may be looked upon as the fine adjustment while the coarse regulation is to be found in the renal function The normal urine is acid in reaction The ingestion of a sufficient amount of base to influence the pH of the blood promptly brings about a diuresis, and an excessive alkaline secretion which may be sufficient to render the urine alkaline On the contrary, if acid substances are ingested, the urine becomes more acid The response of pulmonary ventilation to such changes is instantaneous, while the renal response shows a certain inertia All of these variations of blood pH, pulmonary and renal function can be quite easily demonstrated in the normal man A simpler experiment can be undertaken by voluntarily modifying the degree of pulmonary ventilation Prolonged hyperpnea with atmospheric air will be followed by a period of apnea the length of which will be determined by the interval which must elapse before the pH of the respiratory center has returned to normal There has been produced a condition commonly known as an uncompensated gaseous alkalosis On the contrary, if the inspired air is enriched with carbon dioxide (5 to 10 per cent), increasing pulmonary ventilation may not be able to maintain the alveolar CO_2 at its normal level Therefore there will be a progressive accumulation of CO_2 in the blood and the tissues The excretion of base by the kidneys is rapidly reduced but in the interval there is an uncompensated gaseous acidosis This latter condition is not usually met with in clinical medicine, but the former—uncompensated gaseous alkalosis—often results from hysterical or other neurotic forms of hyperpnea, and may be so pronounced as to produce an alkalosis sufficiently intense to cause tetany

The common terms which are used to indicate these variations in the acid base balance are acidosis and alkalosis They refer however, to changes in the blood rather than to any demonstrable change in cells, although they strongly indicate that such a trend is in operation It would seem best to outline the signs and symptoms of these two conditions and follow with an account of their occurrence in pathological conditions

ACIDOSIS

The first sign of acidosis is an increase in the pulmonary ventilation This takes place through augmentation of the individual respirations In a mild acidosis this may be detected only by the experienced observer, but as it progresses, it is obvious to the least initiated that there is an increased respiratory effort It is commonly known as "air hunger" or "Kussmaul's respiration" The carbon dioxide percentage in the alveolar air is reduced, as is also the CO_2 combining power of the plasma The urine is highly acid and if the renal function is unimpaired will contain large amounts of chlorides phosphates, and sulfates in combination with base Ammonia acting in this capacity will be increased to save the loss of base and the phosphates will

appear as acid sodium phosphates There is also a diuresis and a progressive anhydremia The other signs are headache, anorexia, nausea, vomiting abdominal cramps pains in the limbs weakness, lassitude and coma, with death if the acidosis is severe and prolonged Cyanosis is not present despite the shift of the oxyhemoglobin curve to the right as the hyperpnea maintains a high partial pressure of oxygen in the alveolar air If such a state is maintained more than a few hours irreparable cellular damage occurs, and although the acidosis may be corrected the effects produced are not reversible and death occurs

The causes of acidosis are

(a) Loss of base
(b) Diminished absorption of base
(c) Increased formation of acid
(d) Decreased elimination of acid

The primary loss of base or alkali is a comparatively rare clinical condition but may be due to a loss of pancreatic juice through a fistula persistent vomiting particularly when there is a low gastric acidity and regurgitation of alkaline intestinal contents into the stomach in bichloride of mercury poisoning due to a loss of base in the stools and in children with severe diarrhea Even rarer is the diminished absorption of base It is sometimes encountered in chronic intestinal lesions which lead to diminished absorption but the clinical alkalosis is usually overshadowed by a hypocalcemia probably due to the same cause

An increased formation of acid is the commonest cause of acidosis The simplest example is excessive muscular exertion when there is an oxygen debt and an accumulation of lactic acid in the blood It will be mentioned below how there is in methyl alcohol poisoning a severe acidosis through the formation of formic acid Diabetes mellitus presents a well known cause of acidosis through the formation and accumulation of acetoacetic and β oxybutyric acids derived from incomplete oxidation of fats They are commonly known as ketone bodies and their presence in the blood is called ketosis, and in the urine ketonuria It must not be taken for granted, however that all instances of ketonuria are due to a primary acidosis In severe alkalosis ketonuria may also be present Acidosis of the same character as that of diabetes mellitus may result from a high fat diet or ketogenic starvation particularly in children There are a number of other types of presumed acidosis but whether these are a true bill or not is questionable Ether anesthesia is usually accompanied by signs of a mild acidosis but the exact method of its production if this be actually the case is open to debate There is good evidence to suggest that it might be due to an increase in lactic acid or other unidentified acids a migration of chlorides to the blood or to an excessive retention of carbon dioxide This has not been proved and a decrease in pH precedes the fall in CO_2 It has been claimed that there is a decrease of the alveolar CO_2 and a lowering of the alkali reserve in normal pregnancy but some workers have demonstrated that although the bicarbonate reserve decreases the pH increases, which would suggest that the changes in the blood of pregnancy might be an alkalosis A somewhat similar

the form of sodium bicarbonate, or better as disodium phosphate, may be given but not to the exclusion of more fundamental procedures The direct treatment of alkalosis is more urgent This is best carried out by giving ammonium or calcium chloride by mouth, or weak hydrochloric acid intravenously Calcium gluconate will often remedy the distressing and dangerous tetany J C M

DIABETES INSIPIDUS

Diabetes insipidus is a syndrome usually due to a lesion of the base of the brain, and is characterized by an impelling thirst with a corresponding polyuria The urine is of very low specific gravity and contains no sugar

A great deal of confusion has persisted in the literature as to the fundamental nature of this syndrome, which can be better appreciated if viewed from an historical aspect In 1674 Willis differentiated between diabetes mellitus and diabetes insipidus on the basis of sugar in the urine In 1860 Claude Bernard produce a temporary polyuria with urine of low specific gravity by puncture of the floor of the fourth ventricle Later Schaefer and his associates prepared an active principle from the posterior hypophysis and demonstrated its relationship to a diuresis Farini, in 1913, went a step further and controlled the polyuria of diabetes insipidus by injections of the posterior lobe extract Accordingly he postulated a state of hypofunction of the posterior hypophysis as the causal disturbance In the same year, 1913 Camus and Roussy showed that hypophysectomy itself did not cause a polyuria unless there was an associated lesion of the floor of the third ventricle Finally Richter in 1930, was able to produce a permanent polyuria in rats by puncture of the hypothalamus anterior to the tuber cinereum in the region of the chiasma Thus a syndrome was produced, identical with that in diabetes insipidus by a lesion of the anterior hypothalamus which at the same time was controlled by injections of the posterior hypophyseal extract Today most clinicians consider the diabetes insipidus syndrome to arise from a lesion of the floor of the third ventricle of the brain anterior to the tuber cinereum The lesion may be neoplastic, postinflammatory luetic (tertiary lesion) or traumatic (postoperative) In a study of 107 cases recently reported 63 per cent showed a tumor of the base of the brain, 13 per cent had a syphilitic basis and 8 per cent had a nonspecific inflammatory lesion

Diabetes insipidus may have an hereditary basis as well shown by the studies of Weil Among 119 members of a family, 35 developed the syndrome When hereditary, its onset is usually in infancy or early life, but these individuals may live to old age The syndrome may be transmitted through both parents to both male and female children

From the above it is evident that there are two groups of cases (1) primary" or 'idiopathic ' where the cause is hereditary and (2) secondary ' or ' symptomatic ' where the syndrome results secondary to some organic lesion of the brain The particular part of the brain usually involved is the area just anterior to the tuber cinereum in the floor of the third ventricle The organic lesion is usually a tumor but may be of syphilitic origin, or post inflammatory Rarely the syndrome has followed a fracture of the base of

the skull a cerebral hemorrhage or a basilar meningitis Those cases with an hereditary basis present simply the symptoms characteristic of diabetes insipidus Where there is an associated brain lesion symptoms referable to it are also present

Symptoms—*The symptoms characteristic of the diabetes insipidus syn* drome are polyuria and thirst Polyuria is considered to be primary There is a record of one case where it amounted to 43 liters in 24 hours (Trousseau) The thirst follows as a result of systemic dehydration The onset may be gradual or acute Rarely has a rapid onset been followed by as rapid a dis appearance The urine is pale of a low specific gravity (1 001 to 1 005), but the total solids are not reduced Albumin and other abnormal constituents are not present The kidney function is normal and there is no nonprotein nitrogen retention in the blood Where water is withdrawn the dehydration may become extreme even resulting in convulsive seizures

In the "primary" or congenital type of the disease the syndrome may persist throughout life and the patient live to old age When the symptoms have an organic brain lesion as their cause its nature will determine the outcome Since the majority of these individuals have a brain tumor (usually a glioma), the duration of life is limited to months or a few years depending upon the rapidity of growth of the neoplasm With the progress of the tumor emaciation and asthenia become marked

Pathological Anatomy—The anatomical situation of the lesion in the 'symptomatic' group of diabetes insipidus would seem to be well established in the hypothalamic region The antidiuretic effect of posterior pituitary ex tracts is also well established Whether there is an anatomical and functional relationship between the two is still in doubt but nerve connections have been traced between the hypothalamic area and the posterior lobe of the pituitary via the infundibular stalk

Diagnosis—The diagnosis is not difficult The important point is the in ability of the patient to concentrate the urine even with deprivation of water The diagnostic use of a posterior pituitary extract hypodermically (1 c c) is *of great help in doubtful cases The temporary relief of the thirst with* urinary concentration up to 1 020 or above is characteristic Hysterical polyuria is transitory In chronic nephritis there is a polyuria of low specific gravity (1 006 to 1 010) but the clinical picture with hypertension, nitrogen retention and the presence of albumin and casts in the urine, should dis tinguish the two

Treatment—The treatment of the syndrome should be directed toward control of the thirst and polyuria This can be done with posterior pituitary extracts Unfortunately their effect is transitory four to six hours so their administration has to be repeated Hypodermic administration, by nasal spray or nasal jelly are equally effective The dose must be determined for each indi vidual usually 1 c c three to four times a day is necessary *A dose late in* the evening allows undisturbed sleep More recently pitressin in oil has been made available which has a 24 to 48 hour effect

the form of sodium bicarbonate, or better as disodium phosphate, may be given but not to the exclusion of more fundamental procedures The direct treatment of alkalosis is more urgent This is best carried out by giving ammonium or calcium chloride by mouth, or weak hydrochloric acid intravenously Calcium gluconate will often remedy the distressing and dangerous tetany J C M

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Since the urine has a wide range of reaction there is a marked variation in the percentage of the total uric acid that may be free At a pH of 5 three fourths of the total uric acid excreted is free while at a pH of 8 all of the uric acid is excreted as a salt Normal urine has a pH around 6 at which reaction there are 2 parts of dissolved urates to one part of free uric acid The main bases that participate in the excretion of uric acid as salts are ammonia, sodium and potassium

Uric Acid Metabolism in Gout —In the blood of gouty subjects the uric acid is usually above the normal This elevation is thought to be due to a defective renal excretion of uric acid (Folin) The power to destroy uric acid would not appear to be impaired since in gouty subjects less uric acid is excreted than in the normal individuals when it is ingested as purines

Pratt has shown that between attacks the endogenous excretion of uric acid is less than in his normal controls Just prior to an attack there is an appreciable drop in the urinary excretion during which period the blood value is rising With the initiation of the acute symptoms the urinary excretion increases and the blood reaches its highest concentration At this point the deposition of the sodium monourate crystals takes place. This high concentration of urate in the blood is not the sole cause of the deposition, since there are other diseases such as leucemia and chronic nephritis in which higher blood values occur but deposition never takes place There is some unknown factor which influences this

Etiology.—*Heredity* —Continental and English studies would indicate a high transmission of the gouty diathesis through the male stock Hospital patients in North America have not given such a history When transmitted the abnormality usually remains latent until after thirty five years of age Gout occurs rarely in childhood but when it does occur it is quite severe (See Figs 326 and 327)

Alcohol —Excess consumption of fermented liquors such as wines, beer, porter, and ale, have long been considered to have an etiological relationship to this disease Nevertheless gout is seen in total abstainers Whiskey gin and distilled spirits do not seem to have the same baneful influence

Excess Protein Consumption —Overeating of large quantities of protein food especially meat is considered to break down a latent gouty diathesis Such overeating is usually associated with obesity

Lead Poisoning —Lead poisoning frequently leads to gout This was recognized by Magnus Levy in 1899 who reported 36 cases of gout, 11 of which had definite lead poisoning Multiple joints are frequently involved, and the disease runs a severe course

Symptoms —*Acute Gout* —The acute attack usually has a sudden onset although there may be prodromal symptoms of malaise and indigestion with flatulence The onset is frequently at night, with the metatarsophalangeal joint of one big toe the site of predilection The pain like an "intense burning," causes great restlessness and the toe is extremely sensitive to jars vibration or touch After a few hours as the pain abates the joint becomes reddened swollen with increased local heat The veins are characteristically

More recent studies have shown that the antidiuretic factor is contained in the pressor fraction of this extract, but the therapeutic response when used in a refined form is not superior

There is no advantage in any reduction of fluid intake A slightly restricted salt intake, 3 to 4 grams per day, is helpful

If the primary lesion is luetic, antisyphilitic treatment should be thoroughly carried out Improvement in general health, and rarely almost complete relief of the symptoms may follow Brain tumors of the hypothalamic region are usually inoperable

GOUT

Gout for years has been considered to be an abnormality of uric acid metabolism However we are not certain of the error in the intermediary purine metabolism but later work by Folin has supported the older contention by Garrod, that it is a matter of defective renal excretion of uric acid At recurring intervals uric acid is retained in the blood partly free and partly as a sodium salt When this concentration reaches a certain level an unknown factor initiates the deposition of sodium monourate crystals into and about the joints and tendons, which constitutes the acute attack of gout

That gout may have further basic ramifications would be suggested from the studies of Talbot and his associates, who found that a diuresis appeared before any clinical or subjective evidence of gout was manifest With this diuresis there was a negative sodium and chloride balance

Uric Acid Metabolism—The nucleoproteins of our foods are hydrolyzed in the gastrointestinal tract into the purine substances which are absorbed into the blood stream as such They are quite free from protein phosphoric acid and sugar, which together with the purine make up the original nucleoprotein molecule These purine bases are adenine and guanine which by a process of oxidation in the tissues are changed into uric acid through the stages of hypoxanthine and xanthine Most probably this oxidation takes place in the liver as that organ is the only one from which an enzyme can be secured which is capable of changing xanthine into uric acid As uric acid is an end product in human metabolism it has to be either destroyed or excreted About 50 per cent of that formed in the body is excreted by the kidneys and the balance would appear to be destroyed most likely by the liver That the body can destroy uric acid has not been proved but ingested purines or ingested uric acid can only be accounted for by excretion to the extent of about 50 per cent

Man and the chimpanzee are different from other mammals in their inability to oxidize uric acid The rest of the mammals oxidize uric acid into allantoin to as high as 80 to 98 per cent

The concentration of uric acid in whole blood varies from 1 5 to 2 mg per 100 cc but in serum it is 3 to 4 mg per 100 cc By Folin's later method the normal range may be somewhat higher Free uric acid crystals could never occur at the pH of the blood and other body fluids In the extracellular fluids the main base is sodium thus sodium monourate is the salt formed

prominent There is moderate fever with a slight leucocytosis, and frequently an elevation of blood pressure The duration of the attack is from one to several days, as a rule recurring at intervals of months or years

Chronic Gout—Chronic gout differs from acute gout in that with recurring attacks tophi and bony changes develop that leave a permanently damaged joint There may be a chronic stiffness or a mechanical interference with mobility Frequently bursae become chronically thickened and may even contain crystals of sodium monourate Such cases may have multiple joints involved, the hands elbows knees ankles, etc

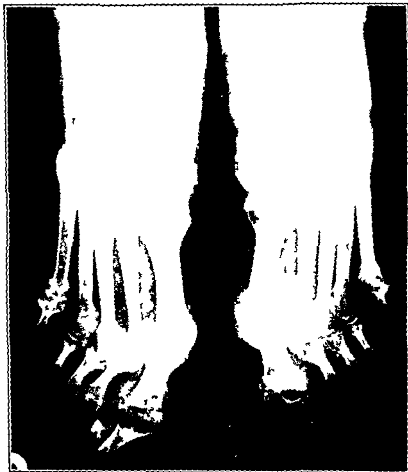


Fig 3 8—X-ray of the feet in a case of chronic gout showing extensive destruction of the metatarsal and phalangeal bones near the articulation, particularly the great toe and the little toe

In addition to the arthritic signs of gout there is an irregular collection of conditions which are attributed to the so called gouty diathesis They are found in members of gouty families who do not necessarily have arthritis The principal manifestations are eczema with fine silver white scales similar to psoriasis which indeed may be also present There are frequently attacks of 'biliousness' or dyspepsia with a foul breath furred tongue constipation and an enlarged and tender liver Migraine, myalgias neuralgias sciatica

Fig 3 6 —A child suffering from [illegible] gout It is important to note the edema of the face the atrophy of the limb the tophi in the fingers and the knees which are conspicuously enlarged (see Fig 3)

Fig 3 —X ray of the knee joints of those shown in Fig 3 6 Note the deposits in the epiphysis of the femur the patella and the periarticular tissues

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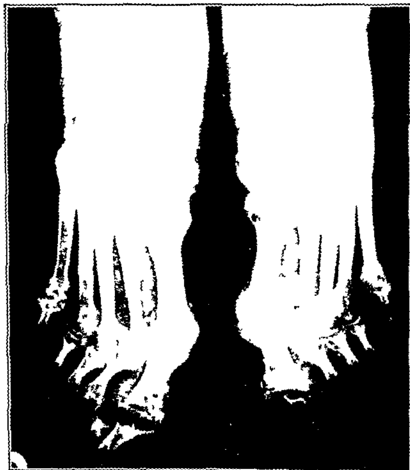


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Fig. 3 6.—A child suffering from severe gout. It is important to note the edema of the face, the atrophy of the limb, the tophi in the fingers and the knees which are conspicuously enlarged (see Fig. 3).

Fig. 32.—X-ray of the knee joints of the case shown in Fig. 3 6. Note the deposit in the epiphysis of the femur, the patella and the periarticular tissues.

An acute inflammatory thickening of the metatarsophalangeal joint of the great toe is very characteristic of gout being the first symptom in a high percentage of the cases This is largely a periarticular involvement due to deposition of sodium monourate crystals in the tissues A thickening of the prepatellar and olecranon bursae may be found



Fig 330



Fig 331



Fig 332

Fig 330—Photograph showing tophi in the ear in a case of chronic gout
Fig 331—Photograph showing a tophus on the finger in a case of chronic gout
Fig 332—Photograph showing tophi on the heel in a case of chronic gout

The blood uric acid is raised in acute gout (4 to 8 mg per cent in whole blood and 6 to 12 mg in serum) and the excretion of uric acid in the urine is increased In chronic gout the blood uric acid may be normal or slightly raised as it will be in intervals between acute attacks

Radiograms of the involved joints are of help Clear areas due to bone absorption frequently occur in the epiphyses but they are not considered to be diagnostic unless they are 5 mm or more in diameter

and other vague but definite pains are common, as are also cramps in the legs Iritis iridocyclitis, and keratitis have been described, and are attributed to deposits of uric acid or its salts Nephroliths composed of uric acid are not infrequent

Diagnosis —The early diagnosis of gout is not easy since the one finding, tophi, that makes the diagnosis certain, does not develop as a rule until five to ten years have elapsed During this interval arthritic pains about joints, cyclic in occurrence, may be the only symptom Examination of the blood for uric acid will usually show it to be raised (above 3 mg per cent in whole blood and 5 mg per cent in serum) Therapeutic trial with colchicum is helpful

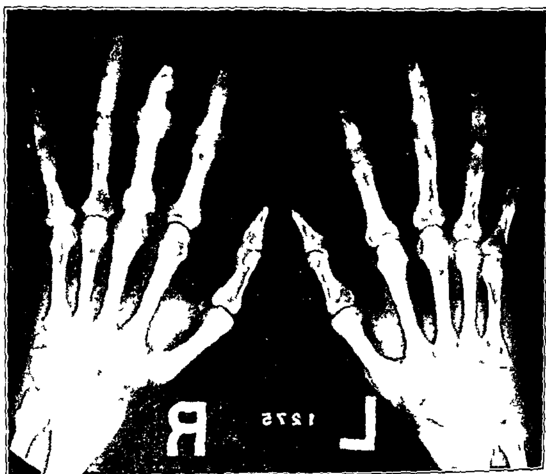


Fig 3[illegible]9 —X ray of the hands in a case of chronic gout showing destruction of the metacarpal bone of the left little finger and the ring finger and the middle phalangeal joint of the right middle finger

Later on the tophi develop They occur on the helix of the ear or about the affected joints fingers or toes They vary in size from a pinpoint to a large marble, and are whitish in color Over the larger ones the skin is frequently ulcerated These tophi are collections of sodium monourate crystals, and their exact identification depends upon the demonstration of the characteristic needle shaped crystals under the microscope

An acute inflammatory thickening of the metatarsophalangeal joint of the great toe is very characteristic of gout being the first symptom in a high percentage of the cases This is largely a periarticular involvement due to deposition of sodium monourate crystals in the tissues A thickening of the prepatellar and olecranon bursae may be found



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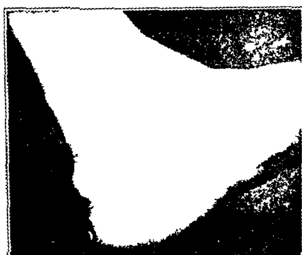


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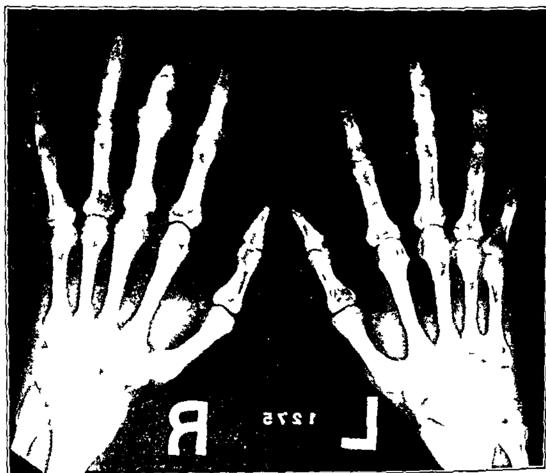


Fig 3 9—X ray of the hands in a case of chronic gout showing destruction of the metacarpal bone of the left little finger and the ring finger and the middle phalangeal joint of the right middle finger

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The use of a purine test meal (100 grams of sweetbreads) given with breakfast, is thought to be of diagnostic help Subsequently the blood uric acid is determined at six, twelve, and twenty four hour intervals Normally it should have returned to the fasting value in twelve hours at the latest This procedure tests the ability of the kidneys to excrete uric acid

A further diagnostic test that has been suggested by Lockie and Hubbard is the feeding of a high fat, low carbohydrate diet to be followed by a low fat high carbohydrate diet Normal people develop a slight rise in their blood uric acid with high fat feeding, but with a low fat diet it rapidly returns to the normal value In the case of gouty patients, the blood uric acid rises with the high fat diet much the same as in normal patients but with the low fat diet the return to the initial level is much delayed

Gout in its early stages, especially before localization about a joint, is frequently not recognized, and the patient is treated symptomatically Shifting joint pains, backache, recurring attacks of lumbago without satisfactory cause should suggest the possibility of gout When there is a localization in or about a joint its differentiation from the various types of arthritis has to be considered The rheumatic fever joint is a fairly clearcut entity occurring in young individuals and usually involving multiple joints The joints of rheumatoid arthritis may offer considerable difficulty, but the deformities x ray changes changes in skin temperature and sweating, and failure to clear up completely are significant The characteristic gouty joint is swollen, reddened with marked sensitiveness of the surrounding skin There may be mild degrees of lymphangitis in acute attacks, but there is little systemic fever As the attack subsides all evidences of inflammation disappear In chronic gout permanent joint changes are found with tophi In doubtful cases of arthritis therapeutic trial with colchicum is helpful While giving prompt relief in gouty arthritis it has little effect in the joints of acute rheumatic fever or rheumatoid arthritis

Complications—In gouty individuals there is a tendency for systemic sclerosis of the arterial tree to develop at an early age This may involve the arteries about the affected joints to a marked degree, seemingly interfering with their nutrition and leading to marked osteoarthritic changes It has been stated that hypertension may occur in gout There is also evidence to strongly suggest that this functional derangement may become permanent and lead to the cardiovascular renal changes described under Hypertension Primary contracted kidneys are a common sequel in gout, hypertension, and lead poisoning Rarely do patients die of gout itself but the outcome depends upon the rapidity of development of the systemic vascular disease Many die in a terminal uremia

Treatment—*The Acute Attack*—In the acute attack the joint involved usually the great toe is extremely tender It should be protected from jars and drafts Colchicum or its alkaloid colchicine should be given to a physiological effect and the diet should be free from purine yielding foods

Dietetic—The diet should be regulated in two particulars First the total caloric intake must be maintained at a level compatible with a normal weight Those individuals overweight should be slowly reduced provided

there is no specific contraindication This means a total caloric intake from 1800 to 2200 calories per day, according to age, sex height, and activity of the patient

Second, care must be taken to control the intake of nucleoprotein which yields the purine substances that are converted into uric acid These foods are meat, fish, chicken, and all internal organs Fruits, vegetables, milk, eggs, cheese, nuts, butter and bread are purine free The nonprotein calories should be given largely as carbohydrate since fat tends to raise the blood uric acid Condiments and spices should be avoided for they stimulate the appetite Alcoholic beverages especially fermented liquors such as wines beer and ale should be strictly forbidden

The use of water should be encouraged in the acute stage up to 4000 c c per day No special value has ever been proved for mineral water of any kind

In the acute phase of the disease a strict observance of a purine free diet is advisable for three to four weeks after which meat, or chicken or fish can be allowed once a day All purine rich foods should be permanently avoided

In the chronic cases some liberty can be permitted as to the purine intake but a permanent restriction helps to prevent future acute exacerbations

Medicinal —Colchicum and its alkaloid colchicine are by far the most useful and safest drugs in the treatment of gout In large doses they relieve the pain of the acute attack and increase the excretion of uric acid in the urine The alkaloid colchicine is thought to be more stable and therefore preferable In the acute attack a dosage of 1 mg for four doses at hourly intervals is usually sufficient to relieve the pain Subsequently two to three doses of 1 mg each per day are required for several days If the wine or tincture of colchicum are used, a dosage of about 2 c c per day is necessary This can be continued for several weeks Since the wine and tincture of colchicum vary considerably in physiological activity the alkaloid is to be preferred The symptom indicating toxicity from colchicum is diarrhea A mild looseness of the bowels is not contraindicated as it indicates that a full physiological effect has been obtained This is desirable

Other drugs such as atophan cinchophen and tolysin have been extensively used but their use is not without some danger In the case of cinchophen toxic necrosis of the liver has been reported several cases have been fatal Sodium salicylate and aspirin are effective in increasing uric acid excretion but have no advantage over colchicum

Prophylaxis —Those who inherit a gouty diathesis may possibly avoid an acute attack by taking care not to become overweight by avoiding excessive alcoholic consumption and by taking a fair amount of out of door exercise

OBESITY

Obesity is simply a state of being overweight This excess weight is due to fat stored in the subcutaneous tissues the omentum and other fat depots If one exceeds his normal weight by more than 10 per cent he can be fairly stated to be mildly obese

Fundamentally the specific cause of obesity is a greater intake of caloric yielding food than there is oxidation in the tissues This positive balance is

stored as fat One must remember that carbohydrate and fat have little specific dynamic action, and that the rate of oxidation in the cell is not appreciably influenced by food eaten The amino acids of protein do cause an appreciable elevation of metabolism in periods of digestion through their specific dynamic

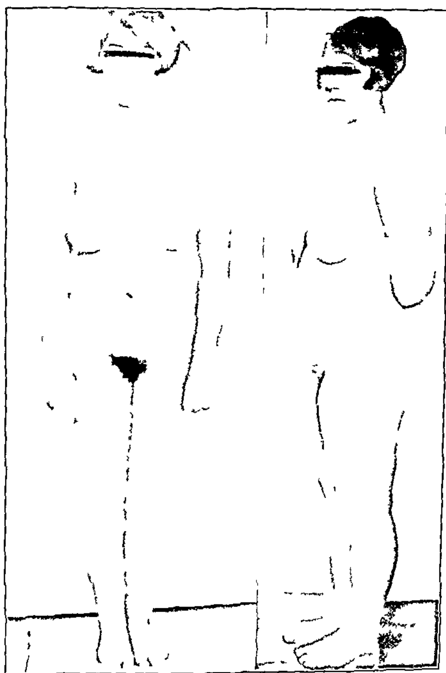


Fig 333 A   Fig 333 B

Fig 333 A—Photograph of a young woman with exogenous obesity Note the general distribution of the subcutaneous fat

Fig 333 B—Side view of the same case as in Fig 333 A

action but people become obese from excess consumption of carbohydrate and fat Obesity develops in most people gradually and after being established interferes with physical activity thereby resulting in a vicious circle It is to

be wondered at that more people do not become obese when one remembers von Noorden's calculation that an excess consumption of but 200 calories a day will result in a gain of 24 pounds in one year

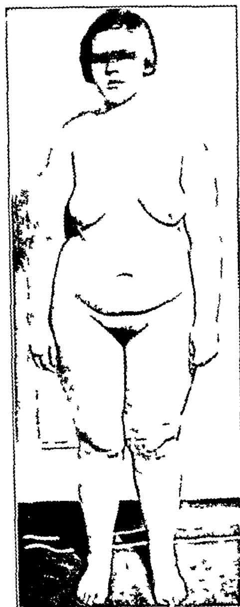


Fig 334 A

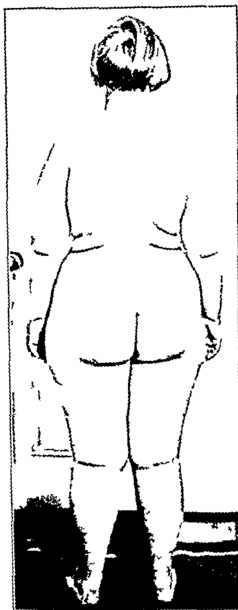


Fig 334 B

Fig 334 A—Pl t [illegible] f [illegible] hil t [illegible] years [illegible] f [illegible] a case of endogenous obesity with signs indicating hypothyroidism and hypopituitarism
Fig 334 B—R [illegible] of th [illegible] a [illegible] in Fig 334 A

Pathological Anatomy —Cases of obesity may be classified into exogenous or simple and endogenous Exogenous obesity includes those cases where the gain of weight is due to excessive eating or decreased expenditure of energy a normal basal metabolism being present In endogenous obesity there is some

endocrine abnormality that results in a lowered rate of oxidation in the tissues which favors a gain in weight

Exogenous Obesity—Means has shown in 41 cases that the basal metabolic rate is normal In the Royal Victoria Hospital a woman with exogenous obesity weighing 385 pounds had a normal basal metabolic rate by the Sage standards Studies upon their expenditure of energy when doing a known amount of work are not extensive enough to rule out the possibility that some cases of exogenous obesity produce less heat than the average normal If this is proved, it may help to explain the gain of weight which at times is baffling As shown by Plaut and others the specific dynamic action of protein may be lessened or absent This again would indicate that metabolic abnormalities which are not understood exist in at least some of these people Further studies from the Royal Victoria Hospital have shown that in exogenous obesity a fatty acid glucose ratio of 3 to 1 in grams can be oxidized without a ketosis which again indicates a metabolic abnormality

In the last analysis the gain or not of weight depends upon the ratio between the total caloric intake and the total metabolism, which is the basal metabolism plus the heat production referable to all physical activity and all endocrine excitants of heat production Recent studies would strongly suggest that the phlegmatic temperament which is usually present in exogenous obesity may influence the total metabolism sufficiently to conserve 100 to 200 calories a day

The tendency in obesity for the tissues to hold water is striking This water retention must be intracellular because there is no pitting edema Whether there is an associated base retention is not known

Endogenous Obesity—Endogenous obesity differs from the exogenous in that there is a lowered rate of oxidation in the tissues due to an endocrine influence This influence falls usually into one of three types hypothyroidism hypopituitarism, or hypogonadism In *hypothyroidism* the fat deposits are characteristically located about the face and neck with the development of the so called 'moon face' Frohlich's syndrome known as *dystrophia adiposogenitalis* is typical of pituitary obesity The fat is in excess about the abdomen hips, and thighs the well known girdle obesity The obesity characteristic of *hypogonadism* is well shown in eunuchs women after the menopause and in castrated animals The deposition is usually general, and in women the lower leg becomes heavier

Symptoms—The symptoms referable to exogenous obesity are in proportion to the degree of obesity Early cases have no symptoms More marked ones would complain of dyspnea and palpitation upon exertion In the very marked cases moderate dyspnea may be present even at rest and activity is associated with so much discomfort that it is practically inhibited

In endogenous obesity symptoms characteristic of the endocrine disturbance would be present as well as those referable to the obesity

Diagnosis—The diagnosis is made by a comparison of the body weight with the standard weight for height age and sex A deviation of plus or minus 10 per cent should be allowed as physiological The basal metabolic rate determination helps to differentiate exogenous from endogenous cases

A study of the diet history over an extended period of time may indicate an excess food intake. The most marked lowering of the metabolism is found in obesity with hypothyroidism. A moderately lowered metabolism is found in obesity with a pituitary or gonad basis.

Prognosis.—Obesity of a marked degree if allowed to remain for an extended period of time materially affects the duration of life. Gradually and progressively systemic arteriosclerosis develops which is later associated with hypertension. Obesity also predisposes to hypercholesteremia which frequently results in gallstones with an associated cholecystitis. Infection of the gallbladder and biliary tract spreads by direct extension into the pancreatic duct with a resulting low grade pancreatitis and diabetes mellitus. So great is the frequency of diabetes in the obese that Joslin has estimated that an individual who is 10 per cent overweight is seven times more liable to diabetes than an individual 10 per cent underweight.

Acute respiratory infections such as pneumonia run a grave course in obesity. Eventually the excessive fat deposits conspire to embarrass the cardiovascular system. There is fatty infiltration of the myocardium, hypertension and a demand for increased cardiac work through increased peripheral resistance with resulting arterial changes (see under Hyperpiesia). Obesity increases the surgical risk of major operations and there is greater danger of postanesthetic complications. The outlook and prognosis for the patient can be materially altered if reduction can be successfully accomplished and maintained.

Treatment.—The fundamental concept in the treatment of obesity is to cause the patients to oxidize their own excess fat depots by supplying a total caloric intake less than their total caloric expenditure. The intake has accordingly to be a subcaloric diet while the heat production can be influenced by exercise, hydrotherapeutic measures and by drugs in special cases. No short cut measures are wise or completely safe in the reduction of the obese. Along with the above a great desire and determination to follow directions or self discipline is essential on the part of the patient.

Exogenous obesity responds to treatment much more readily than endogenous obesity. Accordingly one must be very guarded in the prognosis to individuals with marked obesity on an endocrine basis. It is not safe to attempt reduction in all cases of obesity either exogenous or endogenous. Those individuals showing degenerative changes with myocardial enlargement do not tolerate reduction well. An incipient failure of cardiac compensation may be made acute by too heroic measures.

Rapid reduction by a very low diet, 500 calories per day, is not wise because it is associated with a loss of body nitrogen, a fall in blood pressure, weakness and a greater tendency for the weight to be regained subsequently. A more gradual reduction with a diet of 70 to 90 grams of protein and 1000 to 1200 calories per day gives a much better result. The main part of the nonprotein calories should consist of carbohydrates with a minimum of fat. This avoids mild degrees of ketosis. Great care should be taken to include a minimal supply of inorganic salts and vitamins. The inorganic salt requirement in the main can be met by calcium phosphate supplemented by other elements

as needed. Kelp tablets which contain a variety of inorganic elements have been used to advantage. The diet is usually rich in vitamin C due to its content of fruit juices. Vitamins A, B, and D will be low, and can be given in concentrated form. The choice of protein should be varied, including meat, fish and eggs so that all essential amino acids are included.

Fluid restriction of a moderate degree, 1200 c.c. per twenty-four hours, is helpful and does no harm. Salt restriction, which no doubt accelerates weight loss, is widely employed, but in the writer's experience has at times resulted in a fall of the blood sodium with hypotension. Therefore if practiced, the blood pressure should be watched carefully.

Weight loss should not proceed at a greater rate than 2 pounds a week. Rarely is the weight loss uniform but it takes place at recurring intervals between which are plateaus of a few days' duration, due to water retention. Such periods of water retention can sometimes be overcome by a mild diuretic or by a day of rest in bed during which there will be a marked diuresis.

Exercise, guarded according to the case, is of great help, and makes for a more uniform loss of weight. This can be supplemented by general hydrotherapy and massage.

The only drugs that have a place in reduction, act through stimulating the rate of cell oxidation. The drug most widely used is thyroid extract. In exogenous obesity with a normal basal metabolic rate it should not be used until with the loss of weight there is a moderate fall in the basal metabolic rate. Then it can be used in small doses, sufficient to raise the basal metabolism to normal. However, it must be remembered that protracted administration of thyroid extract tends to suppress thyroid function.

In endogenous obesity thyroid products can be wisely used in sufficient dosage to correct the hypothyroid state. Such patients are frequently very tolerant to large doses of thyroid gland. The writer has seen such cases where 30 grains of thyroid gland (Burroughs Wellcome) per day only raised the basal metabolic rate 1 or 2 per cent. The best results from thyroid therapy are obtained in obesity associated with myxedema.

Due to the difference in physiological activity of various thyroid products care should be taken definitely to specify the product upon the prescription. The iodine content of a thyroid preparation or extract is taken as the index of its biological activity. Although this is not exactly true it is the accepted standard. Different preparations however contain differing amounts of iodine. The following example will illustrate this. Burroughs Wellcome products for use in Canada and Great Britain a thyroid extract which contains 0.3 gm. per cent of iodine according to the B. P. requirement. But they produce for use in the United States a thyroid extract containing 0.2 gm. per cent of iodine (0.17 to 0.23 gm.) to meet the U.S.P. standards. Parke Davis also produces for use in Canada a thyroid extract containing 0.3 gm. per cent of iodine to meet Canadian standards but this is known in the U. S. A. as "thyroid extract strong" to distinguish it from the standard U.S.P. extract containing 0.2 gm. per cent of iodine. It will therefore be seen that there are two official preparations of thyroid extract used on this continent which vary in strength by 50 per cent iodine content.

Other drugs such as dinitrophenol whose specific effect is to raise the metabolism or oxygen consumption are dangerous and should be used only with the closest supervision In the course of reduction a moderate anemia can be corrected by iron preparations At infrequent intervals a saline cathartic helps to remove retained tissue fluid

LIPOMATOSIS

A lipoma is a localized collection of fat in fat cells They occur in areas where fat is normally stored and may be unilateral or symmetrical The nodular lipomas are encapsulated and are classified as nonmalignant tumors

In addition to the circumscribed nodular accumulations of fat a diffuse deposition may be found which again may be symmetrical in its location No definite disorder of fat metabolism has been discovered in these cases and a chemical analysis of the fat has shown no abnormality This diffuse deposition is not a clinical entity but usually occurs in other diseases

For the purpose of clarification a simple classification is best and helps to differentiate these states from the fat accumulations in obesity

Clinical Types—1 *Nodular circumscribed lipomatoses* are not unusual especially in females They cause no symptoms as a rule unless located in a position where they mechanically interfere with function They may be lobulated and tender upon palpation Rarely they cause disfigurement which justifies surgical removal

2 *Diffuse symmetrical lipomatoses (adenolipomatoses)* are nonencapsulated collections of fat which usually are symmetrical more common in males and involve the neck or shoulder regions The degree of fat accumulation may be so great as to produce great disfigurement Frequently there is a symmetrical collar of fat at the base of the neck in the supraclavicular regions Symptoms rarely result Not infrequently scattered throughout the fatty tissue are found small nests of lymphatic glands and more rarely hemolymph glands which justifies the term adenolipomatosis

3 *Adiposis dolorosa (Dercum s disease)* is characterized by symmetrical nonencapsulated fatty deposits which are accompanied by pain asthenia and mental instability They are much more common in women than men and appear especially at the menopause The abdominal wall chest arms and legs may be involved and the skin overlying the fatty deposits is usually hyperesthetic Marked weakness is common This disease tends to run a chronic course and is characterized by remissions

4 *Adipositas cerebralis*—Lesions of the brain may indirectly be the cause of obesity of the endogenous type These fat accumulations have a localized distribution which would justify their mention under lipomatosis

For years Frohlich s syndrome or dystrophia adiposogenitalis has been connected with a pituitary dysfunction with little evidence to justify such an assumption The delayed development of the secondary sexual characteristics might well be related to lack of the gonadotropic factor of the anterior

lobe of the pituitary, but the cause of the associated girdle obesity is still unexplained. Similar types of obesity have been related to lesions of the floor of the third ventricle.

5. *Lipomatosis associated with the pseudohypertrophic form of muscular dystrophy* is well known in this form of muscular lesion and may lead to apparent marked enlargement of special muscle groups due to extensive fatty infiltration of the muscles themselves. These muscles are functionally much impaired.

6. *Lipodystrophia progressiva* is a rare disease starting in childhood, and characterized by a marked emaciation with loss of subcutaneous tissue over the upper half of the body and a disfiguring obesity of the lower half. It is confined to females.

Treatment.—Treatment of all these conditions must be rational. Surgical removal of the fatty tissue may be justified for cosmetic reasons. In those cases where there is an endocrine basis with a lowered basal metabolic rate thyroid products can be wisely used. Pituitary preparations by mouth have never been proved to have a physiological effect.

HEMOCHROMATOSIS

Hemochromatosis (bronze diabetes) is a disorder of metabolism characterized by the deposition of large quantities of the iron containing pigment hemosiderin, in the glandular organs. There is an associated pigmentation of the skin. This pigment deposition especially involves, and is associated with a sclerotic process in the liver, pancreas and spleen. Glycosuria and hyperglycemia are so frequently present that the term bronze diabetes is often used. The syndrome was originally described by von Recklinghausen. No specific cause is known and its fundamental nature is uncertain but there would appear to be a defective excretion of iron.

The onset is insidious, as usually the diabetic state is first recognized. In time the skin pigmentation with enlargement of the liver and spleen lead to a tentative diagnosis which is confirmed as the disease progresses. The diabetic state increases in severity requiring larger and larger amounts of insulin. Malaise, loss of weight, and asthenia follow. The duration of the disease is usually a matter of months, rarely a few years, after it has been recognized.

The anatomic pathological changes are characterized by deposition of pigments in the tissues with fibrotic changes as well as a moderate degree of cellular degeneration in parenchymatous organs. The liver and spleen are enlarged from the sclerotic changes and contain large quantities of hemosiderin. The liver has been found to contain as much as 38 grams of iron (the whole body normally contains 3 grams). The copper content of the liver has also been found to be increased (140 mg. per kilogram). The significance of this copper retention has not been evaluated. The pancreas is usually small and fatty, with varying degrees of fibrosis. The islands of Langerhans may show degenerative changes. Alterations in the parenchymatous cells do not appear to be important but at times the pigment would seem to be causing

direct mechanical damage Hemofuscin, a noniron containing pigment, is found especially in smooth muscle as well as in the heart muscle This pigment contains sulfur, 3 7 per cent and is related to the melanins

The diagnosis is frequently not made until autopsy *The presence of generalized bronze pigmentation of the skin associated with an enlarged firm liver and spleen should suggest the possibility* These findings in a male of middle age with an associated diabetic state would certainly justify a biopsy of the skin Special staining methods show the hemosiderin which settles the diagnosis The blood iron is not increased Hemochromatosis may occur without diabetes Males are much more frequently affected than females *The incidence is about 20 to 1 In a series of 311 cases reported in 1934* the youngest was aged twenty years while the maximum incidence was in the age period between forty five and fifty five years

Pigmentation of the skin becomes deeper and the liver and spleen larger as the disease progresses The associated diabetic state if present may become worse and require increasing amounts of insulin to control the defective carbohydrate metabolism There sometimes develops a certain degree of insulin insensitivity *A moderate hyperbilirubinemia may be found* Weakness gradually becomes conspicuous with a progressive loss of weight In 1927 primary cancer of the liver was reported to be present in 12 out of 128 cases

Treatment—Treatment is without avail to alter the course of the disease Maintenance of weight is difficult due to the extensive liver damage The diabetic condition should be handled in the usual way (see Diabetes Mellitus)

OCHRONOSIS

This is a rare metabolic disorder characterized by a darkening of the cartilages ligaments and fibrous structures everywhere throughout the body The skin also develops varying degrees of pigmentation There seem to be two groups of cases one in which there is an associated alkaptonuria and the other in which there has been a prolonged external application of carbolic *acid preparations When there is an associated alkaptonuria the darkening of the above mentioned structures is due to alkapton formed in the tissues* from homogentisic acid a derivative of the amino acids tyrosine and phenylalanine Why homogentisic acid a normal intermediary product is so changed is unsolved When carbolic acid is the etiological factor the derivative that stains the tissues is unknown

In the first group where there is an associated alkaptonuria the condition is congenital and runs a chronic course Several members of the same family may be affected and it has been known to carry through three generations When associated with carbolic acid poisoning the course may be more acute

The well advanced case presents a characteristic picture of discoloration of the cartilages of the ears and nose with staining of the fibrous tissues and tendons of the knuckles hands and feet *This discoloration may even be* coal black in the cartilage of the nose With its chronic course systemic arteriosclerosis is usually found As the cartilages of the joints are involved

they undergo degenerative changes which gradually lead to osteoarthritic outgrowths arthropathies and deformities

Diagnosis—The diagnosis is not difficult The discoloration of the cartilages, especially of the ear, which is best seen by transmitted light, is of great help The urine, if homogentisic acid is present, causes brown stains on linen which are not removed by soap (alkali) Further the urine will turn brown to black upon standing, or by the addition of alkali When carbolic acid is the causal agent, the history will reveal its prolonged use, usually to the surface of a chronic ulcer However, one must remember that many with alkaptonuria show no staining of their cartilages Excretion of homogentisic acid is increased by a high protein diet, especially when casein is present in large quantities

Treatment—Treatment of the congenital types associated with alkaptonuria is of little avail The excretion of homogentisic acid is lowered somewhat when the diet contains not more than 0 5 gram of protein per kilo body weight which, however is below the minimal biological requirements In the case of carbolic acid its discontinuance will gradually result in a lessening of the cartilagenous discoloration

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CHAPTER XIV

DISEASES OF THE DUCTLESS GLANDS

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INTRODUCTION

In the preceding chapters it has been stated, and more often inferred that the animal organism is not a group of separate systems but a beautifully balanced and coordinated whole which functions in spite of numerous changes in its external and internal environment Its response to these changes operates with a smoothness and rapidity which alone permits of its survival It is true that if they are violent and extreme, a disastrous result may occur but on the whole the power of adaptation is astonishing This indicates a flexibility of function which is governed by factors of the utmost delicacy The role of the nervous system in this regulation is of great importance, but in addition there is a humoral control which depends upon "incretions" or 'internal secretions ' of the ductless or endocrine glands There is hardly a function of the body which is not influenced or regulated by one or more of them Fetal development, birth growth sexual differentiation, development and senescence mental activity and emotional responses are all guided by them In addition nutrition intermediary metabolism digestion cardiac respiratory renal hepatic and hematologic functions are controlled through their influence The interrelations of the nervous system and the endocrine glands are of the greatest importance and the more that is known the more intimate and complex they become

It must be emphasized at the outset that our knowledge of what is commonly known as endocrinology and in a broader sense neuroendocrinology is a subject of comparatively recent date It is true that a fragmentary appreciation that these glands played a role in regulating the organism was suspected and there was considerable theoretical speculation concerning their function This was to some extent clarified by experimental methods through glands being removed from animals and the deprivation effects noted This was a pronounced step forward but when translated to the syndromes met with in clinical medicine it led to an era of the wildest and most unwarranted conclusions which continue to do much to discredit and hamper the progress of this branch of medicine The introduction of biochemical methods and sterol chemistry was required to bring sanity after this orgy of unjustifiable speculations and conclusions and even yet this has not been completely successful Pituitrin and adrenalin were discovered in the final years of the last century but twenty years had to elapse before further progress was made while during the past twenty years the medical world has become almost blasé by the rapidity of new discoveries in this field It has not prevented speculation and premature conclusions outstripping facts Pavlov has placed first in his bequest to the academic youth of Russia—

'Gradualness, gradualness and gradualness! In no sphere of medicine is this more necessary than in endocrinology. We live in an age of speed but this will not hasten Truth to disrobe herself!'

The continued and critical investigations in this field have demonstrated that the incretions of the ductless glands do not act as a simple cause and effect. They are to a certain extent interdependent in that it is through a balance of interaction that a smooth equilibrium is maintained. Further, one gland may not only have what appear to be specific functions of its own but it may also through separate actions either stimulate or retard the function of other glands or organs after a specific manner. This is particularly the case in regard to the pituitary gland which is increasingly being found to occupy a key position in this widespread regulation. Its close anatomical and neurogenic connection with the diencephalon, where are situated so many centers of fundamental importance, would suggest that there is every reason to suppose that the future will reveal an even greater association along both humoral and neurological lines than is suspected at the present. This does not warrant, however, speculation becoming truth or hypothesis a fact.

Many cases will be met with in the practice of medicine where the principal features will indicate what has been taken to be an established clinical syndrome to which a definite name has been given. But as these cases are studied more thoroughly and critically there will emerge undoubted indications of perversions, excesses or reductions of other functions. Their recognition may not be difficult but the reason is by no means always explainable with our present knowledge. Therefore if all cases encountered in the practice of medicine do not fall into the groupings or clinical syndromes dealt with below, it is because combinations and permutations which may arise from the disturbances of function of these glands are of extreme variety. It should be presented that most of the classical clinical patterns, such as acromegaly, Simmonds' disease, Graves' disease, myxedema, Addison's disease, etc., were based upon extreme disturbances of function usually associated with serious and demonstrable anatomical lesions. Furthermore it was considered reasonable that the symptoms and signs were attributable only to the disorder of the gland principally involved. Physiologists would have viewed this concept with some dubiety. There were three concepts which were not given due consideration: First, that there could be a quantitative glandular disturbance within the direction of increase or decrease; secondly, that there might be a multiplicity of activities inherent in each endocrine gland; and thirdly, that these activities could, by affecting other glands or systems, produce quantitative or qualitative results which were secondary to the functions of the original gland where the dominant lesion was situated. It was the failure to appreciate these interrelationships which led to many erroneous conclusions. It will be noted in the following pages that whereas a clinical syndrome was originally attributed to a lesion of one of these glands, it may be imitated by a lesion in another gland through its primary positive or negative effect. This is particularly true of the pituitary gland, but there are other instances, such as the interrelationships of the gonads and suprarenals, the suprarenals and

the pancreas and the pituitary and the pancreas Many of these seemingly interdependent imbalances require much more investigation before a full understanding can be reached J C M

DISEASES OF THE PITUITARY GLAND

Introduction

Anatomy —The pituitary gland is developed embryologically by an upward growth of epithelial cells from the roof of the pharynx which come into contact with a downward extension from the diencephalic floor The epithelial cells, of ectodermal origin, form the anterior lobe, while the glial cells, of diencephalic origin, compose the posterior lobe, and are attached to the midbrain by the infundibular stalk Between the two lobes there is a thin layer of cells known as the pars intermedia In the passage upward of the epithelial cells of buccal origin, a tube of cells is formed, which usually becomes obliterated after contact has been made with the diencephalic downgrowth If these cells persist they may lead to cyst formation and the craniopharyngiomas Eventually the pituitary gland comes to rest in its bony fossa, the sella turcica, and is connected with the midbrain by its infundibular stalk which pierces the diaphragm of the sella The normal pituitary gland measures about 6 × 10 × 14 mm

Early in fetal life the epithelial cells of the anterior lobe differentiate into granular cells which take a stain readily, and are called chromophile cells and those which have a clear cytoplasm, take a stain poorly and are known as chromophobe cells Later the chromophile cells develop either eosinophilic or basophilic granules Normally about three quarters of these cells are eosinophilic and one quarter basophilic The cells of the posterior lobe are of glial origin and are connected with the hypothalamus by unmyelinated nerve fibers passing along the infundibular stalk The secretions of the anterior lobe of the pituitary are emptied directly into the blood stream while those of the posterior lobe may in part pass into the ventricular circulation of the brain

Physiology —Our understanding of the physiology of the pituitary gland is largely based on observations upon the white rat This animal is readily susceptible to hypophysectomy which makes it an ideal preparation for experimental trial with various hormone extracts Fortunately the pituitary hormones are not species specific thus experimental trial and therapeutic use are possible

At present our knowledge of the pituitary hormones may be tabulated as follows

A *Anterior Lobe*

1 Growth hormone (eosinophilic cells)
2 Gonadotropic hormones
3 Thyrotropic hormone
4 Adrenotropic hormone
5 Lactogenic hormone
6 Diabetogenic hormone

B *Posterior Lobe*

1 *Pituitrin*

Pressor action

Oxytocic action

Antidiuretic action

The *growth hormone* is produced by the eosinophilic cells of the anterior lobe It controls normal growth and development of the skeleton and viscera If produced in excess as in the case of the eosinophilic adenoma gigantism results if the epiphyses of the long bones have not united, and acromegaly if they have united The *gonadotropic hormones* are the follicle stimulating hormone (F S H) to the ovary with resulting estrin production In the male it stimulates spermatogenesis The other gonadotropic hormone is the luteinization hormone (L H) which in the female stimulates the thecal cells of the ovary to produce the corpus luteum hormone In the male it stimulates the interstitial cells of the testes to produce the male hormone (testosterone) Thus the gonadotropic hormones control estrin production and indirectly the menstrual cycle in the female and spermatogenesis in the male Also they influence the characteristic secondary sexual development in both sexes The *thyrotropic hormone* influences the function of the thyroid gland If deficient a state of secondary hypothyroidism will develop If excessive hyperplasia of the thyroid with a raised metabolism follows In animals this hyperplasia is limited by the development of an antithyrotropic substance The *adrenotropic factor* acts upon the cortex of the adrenal If lacking atrophy of the adrenal cortex occurs The *lactogenic hormone* (prolactin) influences milk secretion The *diabetogenic hormone* (A P I of Young) has as yet been insufficiently investigated in man In fact there is considerable diversity of opinion as to whether it acts in a direct manner upon carbohydrate and protein metabolism or whether A P I contains some corticotropic hormone which stimulates the adrenal cortex to overactivity which then stimulates the liver to produce hyperglycemia The specific cell of the anterior lobe that makes these hormones is only known in the case of the growth factor

Extracts of the posterior lobe have a marked pressor action upon the blood pressure probably through the intermediary action of the adrenal gland The oxytocic action upon the pregnant uterus is well known Intestinal tone and peristalsis are also influenced by this factor The exact mechanism of the antidiuretic effect of the posterior lobe extracts is not known Therapeutically this factor (antidiuretic) is employed in the treatment of diabetes insipidus

Experimental —Removal of the posterior lobe causes little effect Complete removal of the hypophysis in the immature white rat results in infantilism comparable to the infantilism of a child occurring after destruction of the pituitary by a craniopharyngioma Such animals can be made to grow and develop by daily transplants of fresh exogenous hypophyseal tissue In the mature white rat removal of the hypophysis results in immediate cessation of estrus in the female and genital atrophy in the male The animals lose weight become sluggish and their basal metabolic rates fall to minus 35 per cent or more Atrophy of the thyroid parathyroid and suprarenal cortex follows With transplant therapy improvement takes place

In view of the tremendously widespread influence of the pituitary gland, it has been justly termed the "master gland" From birth to death its normal function controls primarily or secondarily, the skeletal and visceral development, the rate of tissue oxidation of foodstuffs the sexual transformation of puberty and the reproduction of the species The results of changes of pituitary function as to either increase or decrease can be fairly well postulated when they are present to a pronounced degree However much difficulty of assessment may be encountered when the disturbance is relatively moderate in degree which may range over a wide realm This is applicable whether the function is increased or decreased and may be further complicated by the relative secondary effects upon other glands particularly the adrenals and the gonads

Hyperpituitary Function

Gigantism —Gigantism results from a state of hyperfunction of the anterior lobe of the pituitary This hyperfunction is caused by a diffuse hyperplasia or a tumor development of the eosinophilic cells of the anterior lobe.



Fig 33 —Photograph of a pituitary giant and a pituitary dwarf standing beside a man of normal stature (Courtesy of Dr Hector Mortimer)

The tumor is of the adenomatous type and the hormone produced in excess is the growth factor This disturbed function must develop before the epiphyses of the long bones have united to cause the great height characteristic of gigantism There is an associated enlargement of the viscera and other organs

Gigantism frequently starts at the time of puberty with a very rapid skeletal growth during the next few years. If a tumor is the cause, there may be headache and other symptoms referable to pressure upon the neighboring structures. An x ray of the skull may show the presence of an expanding lesion in the sella turcica. Giants are not as strong as their size might indicate and their mental capacity may be below the average.

The excessive production of the growth hormone is frequently associated with a defective output of the gonad stimulating factor which results in sexual immaturity and delay in the closure of the epiphyses. This will extend the growth period into adult years. If the state of hyperfunction persists after growth has ceased the acromegalic syndrome will be superimposed upon that of gigantism. During the period of hyperfunction the gigantic state is progressive but as in acromegaly, a degenerative phase usually follows with a corresponding hypofunction. It is not unusual to find during the hyperactive phase indications of hyperactivity in the other ductless glands such as the thyroid, adrenal, pancreas and gonads. When this has become established the general health is greatly impaired and death follows from some complicating infection.

Treatment—Treatment consists of either surgical removal of the tumor if an adenoma and approachable or x ray therapy. If x ray treatment is instituted early there is a remote possibility of controlling the excess production of the growth hormone since the eosinophilic cells are sensitive to x ray. The effect of x ray therapy upon the production of the other hormones in the growing child is not well established.

Acromegaly

Acromegaly is a disease syndrome referable to an excessive production of the growth hormone by the eosinophilic cells of the anterior lobe of the pituitary. If this hyperfunction develops before the epiphyses of the long bones have united gigantism results; if afterward, acromegaly. In most cases of acromegaly an adenoma composed of the eosinophilic cells is found, rarely is there a diffuse eosinophilic infiltration. The degree of development of the acromegalic state *is directly proportional to the number of eosinophilic cells in the gland.*

The typical eosinophilic adenoma is highly cellular, contains little connective tissue and the cytoplasm is coarsely granular. In time, areas of degeneration and hemorrhage passing on to necrosis develop in these tumors. With such degeneration the earlier state of hyperfunction passes into one of hypofunction with varying degrees of pituitary insufficiency.

Symptoms and Signs—*In its early stages* the excess production of the growth hormone is associated with an insidious enlargement of the hands and the feet. Not until it has been necessary to increase repeatedly the size of the gloves and the shoes is this enlargement called *to the attention of the patient.* At this time a degree of prognathism is usual. Progressively the skin becomes thickened and coarse, the palm of the hand broadens and the facial features coarsen and thicken. Friends may be the first to observe a change in appearance. The skull becomes enlarged with a great prominence of the supraorbital

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The tumor is of the adenomatous type and the hormone produced in excess is the growth factor This disturbed function must develop before the epiphyses of the long bones have united to cause the great height characteristic of gigantism There is an associated enlargement of the viscera and other organs

quality, due to the anatomical alterations of the larynx and head Exostoses are frequent about the terminal phalanges Muscular strength is not in proportion to the hypertrophy of the organs

Headache is usually an early symptom As the tumor arises within the anterior lobe, increased tension is brought upon the diaphragm of the sella with the characteristic pituitary headache With enlargement of the tumor the diaphragm of the sella may rupture with relief of this headache

The eosinophilic adenoma in its early stages is associated with an excess *production of the gonadotropic factor* resulting in menorrhagia and an increased *libido* If the tumor breaks through the diaphragm and extends upward pressure on the optic chiasm may occur with bitemporal hemianopsia and all degrees of optic atrophy Pressure on the hypothalmic *region* will cause polyphagia polyuria, and polydipsia Glycosuria with hyperglycemia occurs in about one third of the cases of acromegaly and this diabetic state is unusually resistant to insulin Early in the tumor growth degrees of erosion of the sella turcica may occur Ultimately this may involve all the clinoid processes and even extend into the sphenoidal sinuses The x ray picture is similar in this respect to that found with the chromophobe adenoma

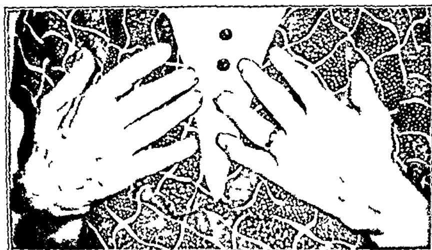


Fig 339 —Photograph of the hands in a case of acromegaly (see Fig 338)

Compression of the remaining pituitary tissue may result in all degrees of pituitary insufficiency Amenorrhea in the female and impotence in the male indicate a defective gonadotropic function

As the tumor undergoes degenerative changes, the state of hyperfunction is changed into one of hypofunction Those skeletal and visceral changes that have already developed persist but muscular atrophy with looseness of the skin occurs with general weakness and asthenia Hyperglycemia and glycosuria may revert to an increased carbohydrate tolerance

Treatment —The *eosinophilic* cells of the pituitary are sensitive to x ray In its early stages before there is evidence of pressure on the optic chiasm intensive crossfire with x ray may cause a shrinkage in the size of the adenoma

ridges and mandible The superior maxillary bones enlarge and the teeth become widely spaced The air sinuses of the skull may develop to huge proportions At this time there is a general macrosomia and macrosplanchnia which includes the tongue Hypertrichosis, with a coarsening of the hair on the head, occurs The sweat assumes an acrid odor, and the voice changes in



Fig 336



Fig 33



Fig 338

Fig 336 —Photograph of a young woman aged twenty-five who subsequently developed acromegaly

Fig 337 —Photograph full face of the same patient seen in Fig 336 aged fifty one after acromegaly is well established

Fig 338 —Profile photograph of the same patient as seen in Fig 337

of a basophilic adenoma which was proved at autopsy Subsequently this syndrome has been described in considerable detail by Cushing, and on this continent it has been termed Cushing's syndrome

The syndrome may occur in either sex, but is more frequent in women It is characterized by (1) an adiposity of the trunk without involvement of the extremities (2) purplish abdominal striae (3) excessive growth of hair on the face (4) plethoric facies (5) hypertension, (6) a tendency for skeletal decalcification with fractures (7) secondary sexual characteristics in the female to revert to the male type (8) transient hyperglycemia and glycosuria and (9) erythrocytosis Amenorrhea occurs in females Rarely does an individual case present the complete syndrome

The exact relationship of this syndrome to a basophilic lesion of the pituitary is not clear Many basophilic adenomata have been reported without the syndrome and more recently the syndrome has been found without a tumor in the pituitary Further this clinical syndrome has been found associated with malignant tumors of the adrenal cortex In fact it would appear that this condition is in the way of being a hyperadrenocorticism either secondary to hypophysial stimulation of the adrenal or due to a primary adrenal lesion (see page 940)

These tumors are not removable surgically X ray therapy has been followed by improvement in a few cases

Hypopituitary Function

Vascular —Deficient pituitary function secondary to a vascular lesion is not as rare as once thought An inflammatory thrombosis of the vascular supply of the gland has been reported This has usually followed an acute infection such as typhoid fever There may be a partial or total cessation of pituitary function according to the circulatory impairment Further the resulting states would be largely influenced by the period in life at which the complication developed If total pituitary lack occurred in childhood an infantile dwarf would result

Postinflammatory —Following infective processes varying degrees of pituitary insufficiency have been reported These may be viewed as the end results of an associated inflammatory involvement of the pituitary gland with resulting fibrosis The syndromes following are comparable to those found after interference with the blood supply of the pituitary gland and in certain cases of Simmonds disease (Compression Syndromes see page 904)

Frohlich s Syndrome (Dystrophia Adiposogenitalis)

Frohlich s syndrome results from a deficiency of both lobes of the pituitary gland It is characterized by a girdle type of obesity and sexual infantilism The sexual immaturity is due to a deficiency of the gonadotropic hormone of the anterior lobe but the cause of the obesity is unknown There is an associated increased carbohydrate tolerance and a moderate lowering of the basal metabolic rate The picture is that of a quantitative reduction of pituitary function

later after the diaphragm of the sella has ruptured, even when visual defects have developed, improvement in sight may follow this treatment If the tumor is causing a progressive loss of sight, surgical intervention may become necessary Since these adenomas are not encapsulated, their removal is difficult and not completely satisfactory Acromegalics are poor surgical risks from the point of secondary complications



Fig 340—X ray of the skull in a case of acromegaly Same case as Fig 3[illegible] Note excessive sinus development

Basophilism

In 1903, Erdheim described two small tumors of the anterior lobe of the pituitary which were composed of basophile cells These growths were of an adenomatous character but there was no associated clinical syndrome In 1931, Teel from the clinical and laboratory findings diagnosed the presence

of a basophilic adenoma which was proved at autopsy Subsequently this syndrome has been described in considerable detail by Cushing, and on this *continent it has been termed* Cushing's syndrome

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Symptoms and Signs—The typical syndrome has its onset in the pre pubertal period Rarely it is seen in adults The obesity is marked about the pelvis and the lower abdomen while the arms and the legs remain normal This is known as the pituitary type of obesity The penis and the testicles are infantile, and at puberty there is a failure of development of the secondary

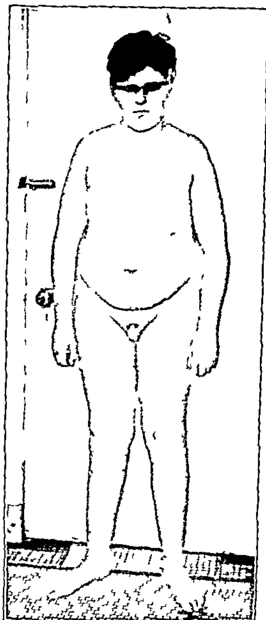


Fig 341—Photograph of Frohlich syndrome in a boy of seventeen years Note girdle obesity sexual immaturity genu valgum Basal metabolic rate −1[illegible] per cent

sexual characteristics The voice remains high pitched in the male, and menstruation does not appear in the female The syndrome having its onset before puberty may disappear with puberty Care should be taken not to diagnose fat children, without due investigation as cases of hypopituitarism Many such suspects at the time of puberty lose their obesity and sexual differentiation proceeds in a normal manner

Diagnosis—The diagnosis before puberty is difficult If puberty is delayed and the syndrome becomes more evident, the situation is clarified The girdle obesity the genital infantilism and the failure of the secondary sexual characteristics to develop, are the main features The basal metabolic rate is lowered (minus 15 to minus 20 per cent) without signs of myxedema, and the carbohydrate tolerance is raised Rarely is there evidence of an intra or suprasellar cyst

Treatment—The literature has reported improvement and cure with the oral use of pituitary preparations that we now know are physiologically inactive The writer has likewise misinterpreted results but now has concluded that "nature" cured the patients at the time of puberty However, today we have physiologically active preparations of the various hormones of the anterior lobe Of these the ones that have given the best results as to growth and maturity have been in our hands a prolonged administration of A P L and the maturity factor of the anterior lobe The dosage has been 1 c c hypodermically of each preparation given on alternate days In a young male with marked delay of sex maturity and growth (5 feet high) treatment was started at 17 years of age His skeletal age was 13 years After three years of treatment his height increased 6½ inches his skeletal age was the same as his chronological age and the sex organs had reached normal development The gonadotropic factor has been used with reported success A word of warning is necessary at this point as all patients do not react satisfactorily, while in others the improvement may be so spectacular as to cast doubt on the correctness of the diagnosis It is not unusual to see cases with puberty delayed beyond the expected age suddenly develop within a few months in a perfectly normal manner without any specific therapy Therefore diagnosis and prognosis should be cautious

Simmonds Disease

In 1914 Simmonds described a state of progressive cachexia developing in an adult due to deficient function of the anterior lobe of the pituitary The syndrome would indicate that all functions of this lobe are in abeyance The anterior lobe of the pituitary may be destroyed by tumors trauma and a variety of local intracranial lesions and has been associated with certain systemic conditions as widely diverse as phosphorus poisoning and hypertension The syndrome has occurred in the prepuberal period from destruction of the anterior lobe by a craniopharyngioma The most important group is that associated with parturition Sheehan and Murdock have made an extensive study of these cases They have found that the most common associated facts are a stormy birth with severe hemorrhage and sometimes infection There occurs a necrosis of the anterior lobe which may vary widely in degree beginning from a small area on the anterior inferior portion under the capsule to a patchy distribution and often complete destruction This is replaced either by fibrosis or a cyst They have attributed the lesion to an arterial thrombosis, but the evidence is not conclusive

The clinical picture in a florid case is most striking There is progressive emaciation with asthenia The average weight of the patients in the published

reports is 90 pounds There is a general microsplanchnia, that of the thyroid and adrenal being functionally most conspicuous The changes in these two organs are essentially atrophy and not a destruction, as in myxedema and Addison's disease In addition to the emaciation there is a wide range of symptoms

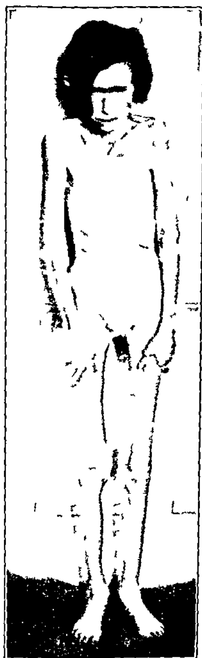


Fig 342.—Photograph front view of a case of pituitary cachexia (Simmonds disease) which began before adolescence

and physical signs They may complain of being always cold and shivering there is mental depreciation they are careless of their persons and habits and suspicious to a degree that may make examination and treatment impossible in fact they may become definitely psychotic The pubic and axillary hair

disappears the teeth may fall out the breasts uterus and external genitalia atrophy as do also the ovaries and testes Libido disappears, and there is amenorrhea

Examination shows a subnormal temperature, a slow pulse, slow respirations and a low blood pressure The uterus is infantile and the breasts atrophic The blood sugar is low verging on hypoglycemia and there is abnormal sensitivity to insulin The basal metabolic rate may be minus 30 to minus 40 per cent The writer has observed a case in a young woman with transient edemas causing a temporary gain of 20 pounds in weight In the less florid cases all degrees of these symptoms may be encountered and in varying combinations This is particularly so in cases following parturition

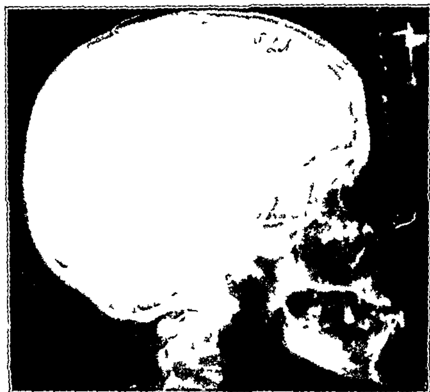


Fig 343.—X-ray of the skull of the case shown in Fig 342 Note erosion of sella turcica by suprasella tumor

It is very probable that many such cases are not recognized as due to partial pituitary destruction and cannot be rightly called Simmonds disease in the sense that he originally described it Emaciation is not always an essential feature of these milder cases in fact increase of weight has been reported in the presence of other symptoms As it may occur in both sexes in a modified degree these cases are not only associated with parturition

The *diagnosis* of the extreme cases is not difficult but they must be differentiated from anorexia nervosa which however usually occurs in adolescence or soon thereafter The general symptoms and signs are quite similar but the

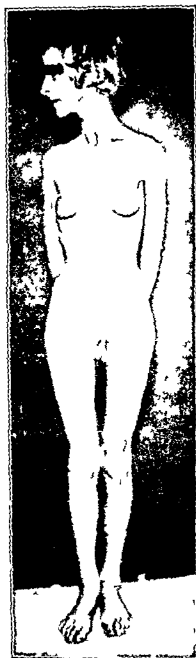
mental disturbances are not. In anorexia nervosa there is often an antedating psychic insult usually of a sexual basis. Hysterical manifestations are more prominent than are those of a psychosis and they are quick and alert in their mental reactions. The diversity of the symptoms in this latter disease may be accounted for through the deleterious influence of starvation upon endocrine functions. The other diseases to be differentiated are hypothyroid function (myxedema) and Addison's disease. In the former the other endocrine deficiencies are not so evident, particularly those referable to the sex hormones.



Fig. 344.—Photograph, side view, of a young woman who took a prize at a beauty contest and subsequently developed anorexia nervosa.

In the latter the specific biochemical changes (see page 936) may give a lead and, if skin pigmentation is present, it would eliminate the pituitary syndrome. It must be appreciated that the picture may be dominated by lack of growth, gonadotropic, adrenotropic or thyrotropic hormones or any combination thereof. But here is presented often a great problem in differentiation between a lesion of the adrenal cortex and of the pituitary, particularly in those cases where the syndrome is only partially developed. The diagnosis may be helped, however, by the determination of the 17 ketosteroids and corticoids in

the urine the Kepler-Power water test and the Wilder sodium chloride test (see page 937) These may be further extended by the estimation of excretion of follicle-stimulating hormone (F S H) to help assess the activity of the



F[illegible] 34 —Front view of th[illegible] same wo[illegible]n a[illegible] in F g 344 after [illegible] suggestive of pituitary [illegible] which were [illegible]eally due to [illegible]

pituitary gland In the milder postpartum cases failure of lactation and amenorrhea should be viewed with suspicion as to the possibility of a pituitary lesion

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Fig 344 —Photograph [illegible] of a young woman who took a prize at a beauty contest and subsequently developed anorexia nervosa

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Fig 345 —Front view of the same woman as in Fig 344 after symptoms suggestive of pituitary cachexia had developed which were really due to anorexia nervosa

pituitary gland In the milder postpartum cases failure of lactation and amenorrhea should be viewed with suspicion as to the possibility of a pituitary lesion

The *course* of the well established disease in the nonparturient cases is usually slowly progressive but may last for years In the less conspicuous cases relative recovery sometimes occurs but in these the anatomical diagnosis is always in doubt

Treatment —In the cases occurring after parturition it is claimed that if pregnancy can occur again by natural or artificial means almost complete recovery will take place provided the confinement is devoid of the original complications of hemorrhage and sepsis Others have reported benefit from pregnancy urine and pituitary extracts, but it is difficult to be certain always that these are authentic results on account of the imitation of so many cases by anorexia nervosa In cases with dominating thyroid deficiency thyroid therapy may be beneficial, and where hypoadrenal deficiency is prominent, cortin might be of value But there are other functional fractions of the adrenal hormones dependent for their stimulus from the pituitary gland which must be taken into consideration These are as follows (1) the salt or electrolyte balance which must be preserved (see page 929) (2) the value of desoxycorticosterone acetate to meet certain specific deficiencies, (3) testosterone is sometimes of theoretical value and should not be neglected as a possible therapeutic agent to meet certain features of the disease (4) finally, it must be appreciated that through the complete absence of the adrenotropic hormone the so called adrenal deficiency crises may occur These should be handled as laid down when the primary lesion is in the adrenal glands themselves (see page 940) J C M

Compression Syndromes

Syndromes resulting from compression of the pituitary gland may result from (1) craniopharyngiomata and (2) chromophobe adenomata

Craniopharyngiomata

It will be recalled that in the process of development of the pituitary gland an epithelial upgrowth takes place from the roof of the pharynx to meet a diencephalic down growth This epithelial stalk forms the anterior lobe and in the process of its being pinched off, cell rests not infrequently remain which by growth and expansion form the craniopharyngioma tumors (Rathke's pouch tumors) These tumors may arise from cell rests above or below the diaphragm of the sella, and vary in size from a small pea to a good sized ball They may be solid or cystic Mature differentiation of the composing cells may follow producing cornification or keratohyaline changes Again there is a great tendency for cystic degeneration with calcification of the walls The cystic tumors contain an oily fluid with an abundance of cholesterol crystals Strictly speaking craniopharyngiomata are not malignant but if they have invaded the grey matter there is no true capsule On account of their position and size, all symptoms and signs are related to pressure effects No hormone production has been observed Their frequency is greatest in the second decade of life

Symptoms and Signs —The earlier symptoms are usually headache and vomiting, most frequently occurring in a child who has shown varying degrees

of defective development Further symptoms depend upon the pressure of the tumor upon contiguous structures From pressure upon the anterior lobe of the pituitary all grades of defective growth and sexual differentiation may follow It therefore should be emphasized that many of the signs and symptoms are to a large extent dependent upon the age at which pituitary deficiency manifests itself This is true irrespective of the original cause Pressure upon the optic chiasm leads to optic atrophy bitemporal hemianopsia and complete bilateral blindness Involvement of the hypothalamic region may result in polyuria polydipsia and hypersomnolence With occlusion of the aqueduct of Sylvius hydrocephalus will occur

Physical examination will show the above symptoms in accordance with the structures involved The temperature is usually subnormal, and the basal metabolic rate moderately lowered Due to the frequency of calcification of the walls of the tumor x ray shows a shadow in approximately 80 per cent of the cases Erosion of the sella turcica and an area in the base of the skull is variable

Treatment—Treatment is surgical If cystic withdrawal of the contained fluid will sometimes relieve the pressure symptoms for one to one and a half years Total removal is extremely difficult Medical treatment should be designed to correct deficient pituitary function, especially the lack of the growth and the gonadotropic hormones

Chromophobe Adenoma

The chromophobe tumors primarily arise from the epithelial cells of the anterior lobe of the pituitary in their early differentiation into chromophile *or granular cells, and chromophobe or cells with a clear cytoplasm The* eosinophilic chromophile cells are known to produce the growth hormone, but no function has been proved to be carried on by the chromophobe cells These cells have a marked tendency to form adenomata which are highly cellular and friable They usually grow slowly and cause symptoms resulting from pressure upon the remaining pituitary tissue and the suprasellar structures Erosion of the sella turcica may be marked with extension even into the sphenoidal air sinuses While the craniopharyngiomata are commonest in early life the chromophobe adenomata develop in middle age The sexes are equally affected Like the craniopharyngiomas the symptoms depend on pressure upon the remaining pituitary gland or upon contiguous structures *Due to their development in a later age* period the resulting syndrome may be markedly different

Symptoms and Signs—As chromophobe adenomata *arise within the ante*rior lobe the early symptoms have to do with increased pressure within the sella turcica Headache "behind the eyes," is thought to be a matter of tension upon the diaphragm of the sella Later as the tumor expands, erosion of the diaphragm occurs and the tumor extends upward The sudden disappearance of headache is considered to be due to rupture of the diaphragm with relief of the intrasellar tension

As the tumor expands in the sella turcica the pituitary gland is greatly compressed with resulting functional deficiency If this happens before

maturity has been reached all grades of defective development, as found in the craniopharyngiomata, may occur. Since the majority of the chromophobe adenomata develop in adult life, the symptoms then have to do with cessation of the gonadotropic function: amenorrhea in the female and impotence in the male. With the rupture of the diaphragm and extension upward of the tumor, pressure on the optic chiasm and hypothalamus occurs. Erosion of the bony walls of the sella turcica and of the clinoid processes tends to occur early and may progress to cause great destruction of the base of the skull.



Fig. 346.—X-ray of lateral view of skull showing extensive erosion of base from a chromophobe adenoma in a male aged twenty.

Treatment.—This is the commonest type of pituitary tumor in which surgical removal is attempted. Progressive loss of eyesight justifies surgical intervention. The results in skilled hands are highly satisfactory. X-ray treatment is of no avail in that the chromophobe cells are not radiosensitive. Replacement therapy for deficient pituitary function should be attempted with physiologically active preparations. This is more imperative in the growing child.

Dwarfism

Pituitary dwarfism is a fairly well defined type of infantilism. Its onset is usually early in life but it is rarely recognized under five years of age. The functional disturbance is in the first instance a lack of growth, and later through deficiency of the gonad stimulating factor of the anterior pituitary, there is no sexual development. Cachexia does not occur. The indi

vidual reaches mature years with the physical development of a child The body proportions are normal for the height, with the sexual organs in proportion Secondary sexual characteristics are absent Development of the reproductive organs in the female is arrested The epiphyses remain open throughout life so slow growth may take place

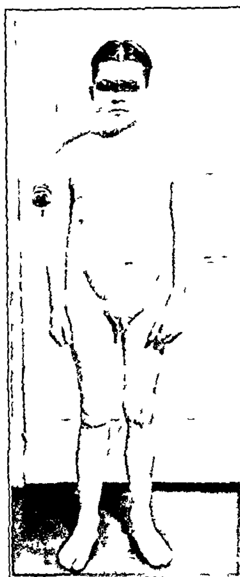


Fig 34 —Photograph of pituitary dwarf aged twenty one and height 4 feet 4 inches

Treatment—Treatment of pituitary dwarfism should be based upon administration of the growth and the maturity factors of the anterior pituitary These must however be given over a period of many years Unfortunately *many preparations of these factors are of low potency or effectiveness* Thyroid or thyroidotropic extract may be helpful Growth can be hoped for only so long as the epiphyses remain open and treatment should not be continued after their closure and sexual maturation

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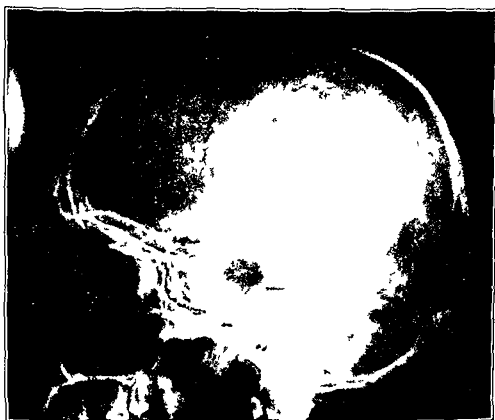


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In the male the pituitary control of thyroid function is probably more uniform than in the female. Thus there is less danger of hypertrophy or involution deviating from the physiological range. This may explain the greatly increased incidence of all types of goiter in the female.

Due to the difficulty in coordinating the pathological histology with the clinical findings many clinicians have considered it wiser to employ a simplified classification. Recognizing these difficulties, the "thyroid group" at the Royal Victoria Hospital for many years has used a descriptive clinical classification which is similar to that recommended by the American Association for the Study of Goiter.

Classification of Diseases of the Thyroid Gland

A. Goiter
- 1. *Adolescent*—diffuse (colloid)
  - —nodular (colloid)
- 2. *Nontoxic*—diffuse (colloid)
  - —nodular (colloid or adenoma)
- 3. *Toxic*
  - Simple—diffuse (colloid type that becomes toxic)
    - —nodular (cystic or adenoma)
  - Exophthalmic—diffuse (Graves' disease)
    - —nodular (Graves' disease that has developed nodules in previous cycles of hyperplasia and involution)

B. Thyroiditis—acute
- —chronic

C. Tumors—benign
- —malignant

Adolescent Goiter (Diffuse and Nodular)

Definition.—Adolescent goiter is a diffuse or nodular enlargement of the thyroid gland occurring in growing children and usually having its onset at the time of puberty. This enlargement is due to an increased colloid storage resulting from iodine deficiency.

Occurrence.—There is a world wide relationship between the incidence of adolescent goiter and the amount of iodine in the soil. Iodine poor soils will result in a deficient iodine content in the drinking water, the vegetables and other foodstuffs. On the North American continent the glacial age resulted in the surface soil being carried southward so that an extensive "goiter belt" traverses the continent from east to west. This "goiter belt" includes the St. Lawrence basin, the Great Lakes basin, the Upper Mississippi valley and the northwest states and provinces. In other parts of the world the incidence of adolescent goiter is high in mountainous districts, such as the Alps, the Peak Country of England, the Himalayas and the Pyrenees, areas which have been denuded of their surface soil and are deficient in iodine.

DISEASES OF THE THYROID GLAND

Introduction

The thyroid gland is derived embryologically as a median evagination of the endoderm of the floor of the pharynx between the first and second pair of pharyngeal pouches. These cells grow downward and ultimately, at the level of the second and third tracheal rings, form two lateral lobes with a connecting isthmus. In the process of forming the lateral lobes, this sausage-shaped tube coils upon itself endlessly like a bag of worms, which accounts for the characteristic picture upon cross section.

As understood today, the specific function of the thyroid gland is to manufacture the hormone thyroxin ($C_{15}H_{11}O_4NI_4$) which is carried via the circulation to all nucleated cells of the body. For the formation of thyroxin, iodine is necessary, the gland using about 0.75 mg. per day. The total tissue content of thyroxin is about 16 mg. With a total cessation of thyroid function the oxygen consumption or basal metabolic rate falls to minus 40 per cent. Thus each milligram of tissue thyroxin would account for about 2.5 per cent of the body's basal metabolism.

The thyroid gland is a very mobile organ undergoing a cyclic change in women from puberty to the menopause. These cycles are a matter of hypertrophy and involution occurring in relation to the menstrual periods. The hypertrophic phase is under the control of the anterior lobe of the pituitary through its thyrotropic factor, and occurs in the premenstrual period. Subsequently as the pituitary stimulation is released, involution follows. For the cycle to complete itself in a normal manner an iodine supply is essential. If lacking or defective, the gland becomes enlarged with increased colloid storage (an exaggerated involution). It has been thought that lack of iodine stimulates hypertrophy to progress into hyperplasia with increased blood supply and a depletion of the stored colloid but this is doubtful. What part the thyrotropic factor of the anterior pituitary plays in carrying hypertrophy into hyperplasia is not known. Experimentally the thyrotropic factor can produce hyperplasia with a raised basal metabolic rate, and if its administration is continued, an antithyrotropic factor develops which neutralizes the thyrotropic factor, with disappearance of the hyperplasia and the raised oxygen consumption. Whether in the toxic goiter there is a failure of antithyrotropic factor control is not known. After total thyroidectomy and in myxedema an increased amount of the thyrotropic factor circulates in the blood. In exophthalmic goiter no increase of the thyrotropic factor has been found in the urine.

Viewing the mobility of the thyroid in this light, the occurrence of colloid goiter is initiated by a lack of iodine which interferes with the normal cycle of hypertrophy and involution, really a matter of excess involution. The nodular colloid goiters may result from involuntary cystic changes or a cystic involution following mild degrees of hyperplasia. The development of toxicity may be determined by the balance between thyrotropic and antithyrotropic factors which would limit the progress of hypertrophy into hyperplasia. This is a hypothesis only; its verity will have to be proved in the future.

table salt should be used The addition of iodine to the drinking water has been instituted without harm if the concentration is within reasonable limits The excessive use of iodine both in salt and water is dangerous Not only is it apt to produce iodine intoxication but it may cause signs of thyroid toxicity School children spring and fall should receive 5 to 10 mg of iodine twice a week This can be administered as sodium iodide hydriodic acid, or in the form of a chocolate tablet (Iodocasein or Iodostarine)

Curative —The results of treatment of adolescent goiter once established have been exceedingly disappointing This statement is based upon extensive experience at the Royal Victoria Hospital in Montreal Iodine results in an increase in intracapsular tension due to increased colloid storage The combination of iodine and thyroid where the basal metabolic rate is low has also given indifferent results Iodine dosage should be small and given in interrupted periods Possibly treatment has prevented some goiters from becoming larger Over 90 per cent disappear spontaneously with maturity Those having a nodular character are more liable to persist and develop into the nodular colloid goiters of middle age

Goiter—Nontoxic

Diffuse —This is a diffuse enlargement of the thyroid gland occurring in an adult, due to increased colloid storage It may have followed an adolescent goiter There are no signs of toxicity, and the only symptoms present are referable to pressure on the trachea The basal metabolic rate is normal or slightly lowered

Its incidence and etiology have the same basis as the colloid goiter of adolescence In time as the gland passes through cyclic phases of hypertrophy and involution with a tendency to increase in size, cystic areas of degeneracy may appear producing elastic nodules These are the colloid strumas so commonly seen among the adult population in goiter districts Intrathoracic extension of these cystic nodules may occur

Complications of the diffuse colloid goiter in the adult are only a mild degree of tracheal compression Their removal is rarely justified due to the probability of a postoperative myxedema

Nodular —Goiters of this type may be nodular from involutional cystic areas of degeneration or from adenomas Most long standing diffuse colloid goiters in adults become nodular and as a rule it is only after their nodular character has developed that they cause pressure complications and require surgical removal

Adenomas of the thyroid are usually unilateral but may be bilateral They may be small or as large as a lemon The very large nodular enlargements without toxicity always contain cystic areas of degeneration

Thyroid adenomas are supposed to be of fetal origin and are capable of becoming toxic Hemorrhages may occur into them, and a few develop malignant changes Others undergo cystic degeneration

Pathogenesis —(Adenomata) It is considered that the adult thyroid gland contains small nests of cells capable of regeneration into tumorlike

Etiology—As the etiology of all types of colloid goiter, both in the child or adult, is the same, it will be discussed at this time There are two main schools of thought as to its cause, one upholds iodine deficiency, and the other an infectious agent The incidence of colloid goiter is certainly greatest where there is a deficiency of iodine in the drinking water and foodstuffs, but McGarrison's studies in India indicate that pollution may be a contributing factor On the North American continent the importance of a lack of iodine as an etiological factor has been amply demonstrated by Marine The prophylactic use of iodine among the school children of the Great Lakes district has tremendously reduced the incidence of colloid goiter, a convincing argument In Switzerland similar results have been obtained

Symptoms and Signs—The enlargement of the thyroid gland develops gradually at the onset of puberty It is usually diffuse but may be nodular and is always bilateral When a colloid goiter especially of nodular type is found in younger children the mother frequently has myxedema Most diffuse adolescent goiters, even if untreated disappear spontaneously with adult years The nodular ones are more liable to persist This increased colloid storage is definitely related to menstruation and becomes more marked at that time In its early stages the diffuse enlargement of the thyroid causes no symptoms The patient's attention may be called to it either by the school nurse or a friend Later especially if the surface is nodular, mild symptoms of pressure on the trachea may be complained of

Upon palpation the gland is usually soft but becomes more tense just be for menstruation If nodular there may be adenomata or involutional cysts

The basal metabolic rate is moderately lowered in about 50 per cent of these young people It is common for it to range from minus 15 to minus 20 per cent They present no definite symptoms or findings of myxedema One should consider the condition a secondary hypothyroidism

Anatomical and Functional Pathology—The enlargement of the thyroid gland is due to a distention of the acini with colloid which stains normally in microscopic sections This distention may result in a flattening of the cuboidal cells lining the acini The nodular character is usually a matter of an involutionary cycle which has followed a previous period of mild hyperplasia Rarely circumscribed adenomata of fetal origin may be present This colloid storage is viewed as a resting stage but again it would appear to be related to a deficiency in iodine available for the normal completion of the active secretion thyroxin Since the thyroid is enclosed within a capsule the colloid storage would increase the intracapsular tension producing mild tracheal irritation and compression

Diagnosis—The diagnosis of adolescent goiter is simply a matter of inspection and palpation The enlargement is bilateral and nodules can be best palpated by lateral displacement of the trachea A careful history and physical examination will exclude a toxic goiter The basal metabolic rate is never raised but is usually slightly below the normal

Treatment—*Prophylactic*—Preventive treatment of adolescent goiter is far more satisfactory than curative treatment In all goiter districts iodized

of a recurrent laryngeal nerve produces a characteristic hoarseness of the voice until the other vocal cord compensates Mediastinal obstruction may produce great venous stasis in the vessels of the neck and upper extremities through pressure upon the superior vena cava Further, as the gland assumes a grossly nodular character the nodules may compress the remaining normal tissue leading to a certain degree of functional deficiency

Treatment—In the case of involutionary nodules surgical removal is justified to relieve pressure Following their removal the basal metabolic rate if it has been depressed, has been observed to rise appreciably, suggesting release of pressure upon potentially normal tissue Small nodules, cystic or adenomatous, do no immediate harm Potentially the adenomata are capable of developing an abnormal activity, or becoming carcinomatous The onset of hyperthyroidism usually is insidious and material cardiac damage, even auricular fibrillation may develop before it is recognized Therefore care must be taken to follow developments at regular intervals if removal is deferred If the nodule is large enough to cause symptoms from pressure or pressure without symptoms, it should be removed Until recent years many surgeons were content with unilateral operations with the result that five to ten years later the patient returned with a similar nodule in the other lobe Careful examination at operation will usually reveal bilateral nodules which justify a bilateral thyroidectomy

Goiter—Toxic

Until recently a distinction was drawn between the nature of the toxicity in the nodular (toxic adenoma) type and that of classical exophthalmic goiter It was suggested based in part upon their response to iodine that the toxic adenoma of Plummer was a pure hyperthyroidism while the toxicity in exophthalmic goiter was due to some incompletely iodinized molecule or dysthyroidism Later the response of both types to iodine was shown to be practically the same Further the work of Rienhoff and others strongly points to the conception that both conditions result from the cycles of hypertrophy hyperplasia and involution

Simple—Diffuse—Rarely does a diffuse colloid goiter become toxic without becoming nodular The writer over a period of many years observation has seen one such case which followed excessive thyroid therapy in a young woman with a simple colloid goiter After withdrawal of the thyroid medication the toxicity continued in a severe form with an increase of 40 per cent in the basal metabolic rate A bilateral subtotal thyroidectomy was done The sections of the removed tissue showed marked hyperplasia without stainable colloid No eye signs developed

Simple—Nodular—This is the toxic nodular goiter without exophthalmos The typical picture has been well described by Plummer under the caption Toxic Adenoma A nodular enlargement of the thyroid is present for five to fifteen years An increase in the size of the nodule gradually or suddenly occurs There develop at the same time nervousness tremor palpitation and loss of weight The gland shows a moderately increased vascularity The basal metabolic rate increases by 30 to 100 per cent Myocardial changes and

nodules The cells composing these nests may be fetal or fully differentiated in character The nodular growths arising from the fetal cell nests are termed fetal adenomata, while those developing from the differentiated cells are termed simple adenomata The factor that initiates this cell growth has been postulated as a lack of iodine Adenomata arising from the mature cell show some attempt at capsule formation, while those developing from the fetal cells are usually multiple, have no colloid, and little supporting stroma Cycles of hypertrophy and involution occur in these adenomata as in the rest of the thyroid tissue Their cells are thus subject to hyperplasia and cystic degenerations Necrosis of their central areas is not unusual



Fig 348 —Photograph of a patient with nodular nontoxic goiter

Symptoms—(Adenomata) Usually a moderate enlargement of the thyroid has been present from five to ten years when a lump is observed to develop in one lobe This nodule may increase in size slowly or rather rapidly Palpation frequently shows the presence of multiple nodules They are always movable, and may produce symptoms through pressure upon the trachea, recurrent laryngeal nerve, or esophagus

Complications—If the nodular, cystic enlargement of the thyroid compresses or dislocates the trachea sufficiently stridor may develop Paralysis

of weight soon follows, due to the accelerated oxidation The intake of food fails to supply the requirement, with the result that the balance is taken from the tissues The patient is intolerant of heat Diarrhea may occur periodically and seems to be due to an increased motor activity of the intestines

Examination of the patient shows an anxious, jumpy restless individual who is constantly occupied usually with little purpose The expression is staring and the eyeballs appear shiny A varying degree of exophthalmos is present which may be unilateral, but is usually bilateral The skin is warm and



Fig 49—Photograph of a patient with exophthalmic goiter who postoperatively developed a mild degree of myxedema Note exophthalmos and facial appearance

moist which increases loss of heat by radiation conduction and evaporation of water In that way hyperthermia is avoided The extended hands show a fine tremor an important and constant finding in this condition The pulse is rapid but regular and its rapidity is in proportion to the toxicity This is one of the few conditions with tachycardia in which ventricular extrasystoles occur The pulse pressure is high (80 to 100 mm Hg) with a low diastolic pressure and a capillary pulse is usually present The heart sounds are loud and slapping in character Usually the thyroid gland is bilaterally enlarged soft in consistency (if iodine has not been administered) and a throbbing pulsation can

sometimes auricular fibrillation may occur In fact symptoms of circulatory failure may dominate the clinical picture and come on suddenly Exophthalmos *does not occur* "Toxic adenomata" respond well to iodine, and after being so prepared a bilateral subtotal thyroidectomy should be done Recovery is excellent, and the tendency to regenerate is not so great as in exophthalmic goiter Provided the heart has not been seriously damaged, the prognosis is good

Goiter—Exophthalmic, Diffuse and Nodular

Graves' Disease, Basedow's Disease

Definition—Exophthalmic goiter is a disease characterized by an accelerated state of tissue oxidation, and hyperactivity of the autonomic nervous system The cause is unknown but seems to rest outside the thyroid gland

Etiology—Studies upon the cause of exophthalmic goiter have not produced a satisfactory explanation Many cases would seem to have a relationship to focal infection the tonsils being especially incriminated Nervous shock or prolonged strain has preceded the onset of others The idea that the sympathetic nervous system is in some way driving the gland to hyperplasia and hyperfunction has been suggested but no conception of the factor which initiates the stimulation has been offered In exophthalmic goiter hyperadrenalemia is present in some cases but not invariably so Its significance is not known The idea that the toxicity is a dysthyroidism rather than a pure hyperthyroidism is losing favor Experimentally in animals the complete picture, with the exception of the exophthalmos, has been produced by giving large amounts of thyroid extract or thyroxin The factors determining the development of the exophthalmos are unknown

With the later knowledge of the pituitary influence upon the thyroid through its thyrotropic factor a new conception is being formulated This assumes that the thyrotropic factor is capable when unrestrained, of causing hyperplasia with hyperfunction This conception is supported by certain facts (1) experimental evidence that the thyrotropic factor can temporarily cause hyperplasia with a raised basal metabolic rate (2) the high incidence of exophthalmic goiter in young women in whom one might expect to find instability of the cycle of hypertrophy and involution This conception does not satisfactorily explain the disturbance of the autonomic nervous system other than as a secondary effect of the hyperthyroidism The exophthalmos is not explained Evidence that exophthalmic goiter is not a primary disease of the thyroid gland is the fact that thyroidectomy does not cure the disease The basal metabolic rate may return to normal, and many symptoms disappear but a nervous instability persists Exophthalmos is frequently not influenced by thyroidectomy The thyroid gland also shows a marked tendency to regenerate after its partial removal and the new tissue shows hyperplasia with hyperfunction

Symptoms and Signs—The classical symptoms of exophthalmic goiter are nervousness, irritability tremor and palpitation These symptoms are referable to the state of hyperactivity of the sympathetic nervous system The palpitation occurs at rest and is exaggerated by excitement and activity Loss

of weight soon follows, due to the accelerated oxidation The intake of food fails to supply the requirement, with the result that the balance is taken from the tissues The patient is intolerant of heat Diarrhea may occur periodically and seems to be due to an increased motor activity of the intestines

Examination of the patient shows an anxious, jumpy, restless individual who is constantly occupied usually with little purpose The expression is staring and the eyeballs appear shiny A varying degree of exophthalmos is present, which may be unilateral but is usually bilateral The skin is warm and



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moist which increases loss of heat by radiation conduction and evaporation of water In that way hyperthermia is avoided The extended hands show a fine tremor an important and constant finding in this condition The pulse is rapid but regular and its rapidity is in proportion to the toxicity This is one of the few conditions with tachycardia in which ventricular extrasystoles occur The pulse pressure is high (80 to 100 mm Hg) with a low diastolic pressure, and a capillary pulse is usually present The heart sounds are loud and slapping in character Usually the thyroid gland is bilaterally enlarged soft in consistency (if iodine has not been administered) and a throbbing pulsation can

be seen Upon palpation the increased vascularity produces a thrill which can also be heard Infrequently the thyroid is not enlarged in states of hyper thyroidism In connection with the exophthalmos there are three signs of classical importance which are due to the anterior displacement of the eyeball Stellwag's sign is the lack of winking Moebius' sign is a weakness of con vergence, and von Graefe's sign is the lag of the upper lids upon rotating the eyeballs from an extreme upward position downward

The basal metabolic rate is raised in proportion to the degree of hyper thyroidism Values of plus 25 to plus 50 per cent are found with moderate degrees of toxicity, while above 50 per cent the hyperthyroidism is severe The blood cholesterol is lowered (normal 200 to 225 mg per cent) and varies inversely as the basal metabolism Glycosuria, associated with hyperglycemia, is frequently present in the digestive periods The fasting blood sugar is al ways normal but the glucose time curve may be identical with that of a mild diabetic due to delayed storage of glycogen in the liver A fawn colored cutaneous pigmentation is not uncommon

In the severe cases of exophthalmic goiter the pulse rate may become very rapid 140 to 160 per minute and the basal metabolic rate rise to 75 to 100 per cent above normal Gastrointestinal crises and auricular fibrillation may occur These 'crises' require active treatment, and may result in death from exhaustion or cardiac failure

Anatomical and Functional Pathology—The thyroid gland is diffusely enlarged soft and vascular If iodine has been administered the gland may be firm and its surface slightly nodular from excessive colloid storage Glands in long standing cases of toxicity are frequently nodular, due to involutional changes If iodine has not been given the histological appearance is that of hyperactively functionating tissue The acini are small and contain little stainable colloid Their cells show marked hypertrophy with infoldings of hyperplasia in places filling the lumen This hyperplasia may be patchy or diffuse In addition there is an extensive small round cell infiltration After iodine has been given the picture is that of a tissue trying to revert to the resting state The acini assume more nearly their normal appearance and contain larger amounts of stainable colloid Hyperplasia largely disappears although patchy areas may be found The acinar cells become more cuboidal or compressed by colloid The small round celled infiltration is not so marked

The thymus is enlarged in more than 50 per cent of deaths from hyper thyroidism The myocardium frequently shows degenerative changes and the muscles of the eyes fatty infiltration In long standing cases of exoph thalmos an increase of the retrobulbar fat is found Diffuse lymphoid hyper plasia is present and the blood shows a relative and absolute lymphocytosis

Diagnosis—The diagnosis of the fully developed case of exophthalmic goiter offers little difficulty It is the incipient or concealed type that may be problematical A careful analysis of the symptoms the age and sex of the patient, the presence of an enlarged vascular thyroid and bilateral exoph thalmos are important points Rarely does the incipient case present more than a few of the symptoms and signs A warm moist skin and slight tremor of the extended fingers should not be overlooked There may be neither

exophthalmos nor a palpable thyroid gland In hyperthyroidism the plasma cholesterol is lowered proportionately to the elevation of the metabolism The fasting blood sugar is always normal but the digestion figure may be raised (120 to 200 mg per cent) A glucose time curve will suggest a mild diabetic state due to delayed storage of glycogen in the liver

A raised basal metabolic rate that corresponds with the pulse rate at rest is the most important single laboratory finding With the simplified means of measuring the basal metabolism (oxygen consumption) so generally used clinically care must be taken in the interpretation of the results In the nervous apprehensive patient the first test is almost always too high Most errors of technic (leakage etc) tend to raise the oxygen consumption Careful scrutiny of the character of the respiratory curve is of great help in differentiating the respiratory neuroses associated with anxiety states and hysteria from true hyperthyroidism Respiratory irregularities of rate and depth are indicative of these (see Figs 106 and 108) In doubtful cases repetition of the test will ultimately give comparable results An increase in basal oxygen consumption may occur independently of hyperthyroidism as in leucemia with a pronounced leucocytosis rapidly growing neoplasms or numerous metastases where there is great cellular activity in fevers with an elevation of body temperature (one degree Fahrenheit raises it 7 per cent) in circulatory failure with dyspnea when it may be increased up to 20 per cent from the extra work required for respiration and in all conditions where there is increased muscle tone or gross tremors which cannot be controlled When there is any doubt about the validity of the result it should be checked with the Douglas bag and gas analysis which will give a result less subject to the multiple errors of the ordinary oxygen consumption technic The respiratory quotient (R Q) will be of aid in certifying to an accurate result

Cases of early pulmonary tuberculosis may have nervousness tachycardia and loss of weight but their basal metabolism is normal when afebrile Persons with respiratory neuroses offer the greatest test of diagnostic skill The symptomatology is identical but the skin of the hands and feet is cold and clammy The respiratory curve is irregular as to rate and depth (see Fig 106) The true basal metabolic rate is normal Cardiac decompensation without cause (rheumatic arteriosclerotic or syphilitic) should always be suspected as due to a latent hyperthyroidism Similarly hypertension with a low diastolic pressure may be due to a similar cause

It would seem obvious that in addition to the clinical factors in the recognition of disturbed thyroid function certain metabolic and biochemical tests are most helpful but under some conditions these do not give a specific answer as to presence and degree of thyroid toxicity Recently such a specific answer has been much helped by two additional tests The first of these is the estimation of the serum protein bound iodine This is increased in proportion to the degree of true thyrotoxicosis and contrarily decreased in thyroid deficiency The second test is through the use of radioactive iodine When this is administered there is a greater uptake and retention in proportion to the degree of thyroid activity It should however only be used in selected cases and under properly controlled laboratory conditions

be seen. Upon palpation the increased vascularity produces a thrill which can also be heard. Infrequently the thyroid is not enlarged in states of hyperthyroidism. In connection with the exophthalmos there are three signs of classical importance which are due to the anterior displacement of the eyeball. Stellwag's sign is the lack of winking, Moebius' sign is a weakness of convergence and von Graefe's sign is the lag of the upper lids upon rotating the eyeballs from an extreme upward position downward.

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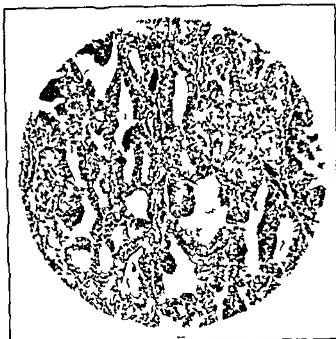


Fig 350



Fig 351

Fig 350 —Photograph of a microscopic section of thyroid gland from a case of exophthalmic goitre before the administration of iodine. (×130)

Fig 351 —Photograph of a microscopic section of thyroid gland from a case of exophthalmic goitre after the administration of iodine (×130)

Complications—Foci of infection should be eliminated if possible, as they may increase the severity of the hyperthyroidism Glycosuria is common during the digestive period It must not be confused with true diabetes mellitus which may be found with exophthalmic goiter Prolonged hyperthyroidism places a great strain upon the heart Dilatation and auricular fibrillation occur but not as frequently as in the nodular toxic goiters which are undoubtedly of longer duration, and therefore the cardiac failure occurs in the more advanced age period, and is fraught with greater danger Exophthalmos, if marked, is associated with edema of the conjunctivae, and inability to cover the cornea may allow physical trauma Ulceration and rupture of the eyeball occur occasionally Optic neuritis is a rare complication At operation injury of the recurrent laryngeal nerve will cause a paresis or paralysis of a vocal cord with hoarseness Such a paralysis may occur due to pressure of the goiter Therefore a laryngeal examination should be carried out in all cases before operation, as a bilateral paralysis will cause alarming respiratory obstruction Postoperative myxedema of varying severity may occur, or it may develop after the acute stage has disappeared spontaneously

Treatment—The treatment of exophthalmic goiter requires in the first instance physical and mental rest This can best be accomplished in a hospital away from the home and relations Maintenance of nutrition is important A high carbohydrate diet is well tolerated and helps to maintain the glycogen content of heart muscle and liver Lactose up to 100 grams a day can be given in fluid drinks On account of the raised metabolism, the total caloric requirement is twice that of the normal (3 000 to 4,000 calories per day) The calcium intake (milk) should be increased, since it has been shown that with hyperthyroidism a negative calcium balance occurs at the expense of the bone calcium Water should be given freely Sedative mixtures of phenobarbital or phenobarbital and sodium bromide help to bring quiet to the excitable nervous system

Medical Treatment—Only the very mildest cases of exophthalmic goiter should be handled by prolonged medical treatment Provided financial resources are adequate and time of little importance, prolonged bed rest and semi invalidism may control the intensity of the symptoms until the disease runs its course Throughout such periods the heart should be watched carefully to detect any dilatation or transient irregularity The sympathetic depressant ergotamine tartrate (gynergen) has been used successfully The dosage varies up to 10 mg per day by mouth

Surgical Treatment—Subtotal thyroidectomy is a means of controlling exophthalmic goiter not a cure To establish a cure in the full sense of the word it will be necessary to discover the primary cause and rectify it There is no field of medicine where teamwork between physician and surgeon is of greater benefit than in the handling of a patient with a toxic goiter Preliminary ligations and partial thyroidectomies are not necessary if certain precautions are observed Iodine in any form should be administered only after a decision has been arrived at that an operation is advisable If this precaution is taken and carried out the mortality from thyroidectomy will be lower In hospital clinics the iodine fast patient is the dangerous and difficult one

At the end of that period an attempt can be made to lower the toxicity by giving iodine again The dosage will have to be larger to obtain a remission Thyroidectomy should be performed after a moderate remission has occurred, as a pronounced one is not to be expected

The technic of subtotal thyroidectomy is fully described in textbooks on surgery *There is, however, one point of extreme importance, namely, that it is better to remove too much thyroid tissue than too little*

X ray Treatment —*The results of x ray treatment are no better than* those from surgical treatment X ray should be reserved for those cases refusing surgical intervention In the case of regeneration after thyroidectomy x ray has a valuable place The exophthalmic goiter that regenerates after a bilateral subtotal thyroidectomy will frequently regenerate after a second operation By the use of x ray we have been able to control the toxicity associated with the regenerated tissue avoiding the possibility of multiple thyroidectomies

Thiourea Therapy —In recent years through the work of Astwood and his co-workers another method of *medical treatment has been evolved This has been the use of thiourea and related compounds* such as *thiouracil methyl thiouracil* etc These latter have much less toxic properties than the former They are considered to act through the reduction in formation of thyroxine They can be used for two purposes First if for any reason it seems unwise to prepare for operation with iodine and a longer period of rest and control is indicated this can be accomplished by bed rest symptomatic treatment and the use of a thiouracil compound in dosages of 0 1 gm four to six *times* a day In *seven to ten days indications of reduced thyroid toxicity will be evident* and will be progressive with a return to normal in four to six weeks Operation may now be indicated or second the drug may be continued in reduced amount of 0 1 to 0 2 gm daily indefinitely After six to eight months it may be stopped and in a considerable number of cases the remission may continue indefinitely with no more evidence of a relapse than is found after thyroidectomy

The *toxic effects of the newer compounds are comparatively rare* and consist of fever skin rashes and severe granulocytopenia *Knowledge of their* possible occurrence and close observation should render them of little danger

Another possible advance in the medical treatment of thyrotoxicosis is the use of radioactive iodine This however is at present in the realm of exploration and should await further knowledge and experience

Thyroiditis

Acute thyroiditis is an inflammation of the thyroid gland It may be a simple productive swelling or a definite exudative process from invasion with pyogenic organisms A primary bacterial infection of the thyroid is rare More *frequently it is secondary to a systemic or pyemic process* Tuberculosis of the thyroid is never primary

The symptoms of an acute thyroiditis are *painful swelling of the gland* with increased heat and extreme tenderness Usually it is bilateral *Moder*

to handle successfully. This state of over iodinization results from prolonged iodine administration. A patient's first response to iodine is always the best.

The Use of Iodine.—*After the decision to do a thyroidectomy is reached* iodine should be started in 5 minim doses, three times a day with meals. Lugol's solution (5 per cent iodine and 10 per cent potassium iodide) is most widely used. After about three days, the pulse will begin to be slower, and improvement in other symptoms follows with a falling basal metabolic rate. The maximum improvement is obtained in ten to twelve days, and thyroidectomy should be done at this time, or just before the period of maximum improvement, when the basal metabolic rate is dropping. This remission will last for a few days

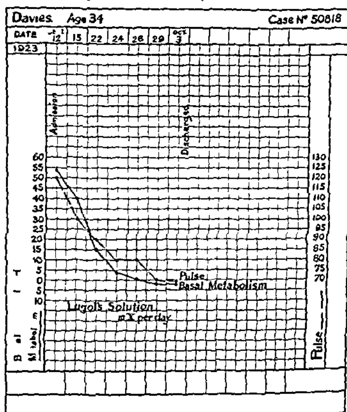


Chart XXX.—The effect of iodine upon the basal metabolic rate in exophthalmic goiter

only, and subsequently the hyperthyroidism in all its features will gradually recur except that the weight may continue to increase. The cause of the remission is not known but Marine has suggested that the increased colloid storage increases intracapsular tension to a point where less blood flows through the thyroid gland with a lowering of the systemic toxicity. In time the circulation reestablishes itself at a higher level of intracapsular tension and toxicity recurs. If the patient has received iodine for an extended period of time and is iodine fast the thyroid will be tense frequently slightly nodular, and signs of toxicity will be present. All iodine should be discontinued for one month and the patient kept in bed under the influence of sedatives

Myxedema

Definition—Myxedema is a disease that develops in adults, due to a primary deficiency in function of the thyroid gland. The defective secretion of the gland results in a lowered thyroxin content of all nucleated cells with far reaching secondary manifestations. Myxedema may result from a primary atrophy of the gland, or secondary to a thyroidectomy or a thyroiditis.

Etiology—Spontaneous myxedema was first described by Gull in 1873. Up until recent years its prevalence was not appreciated. Mild forms frequently exist for many years without a correct diagnosis. The personal history will frequently not explain the cause of the atrophic thyroid state. The

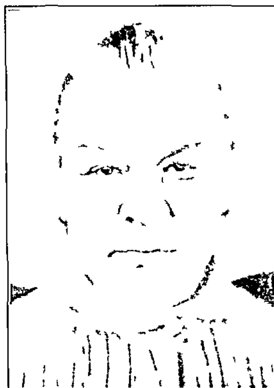


Fig 35 —Photograph of a case of myxedema. Note the thickness of the lips, puffing about the eyes, the scanty hair and the dull expression.

occurrence of the disease secondary to a subtotal thyroidectomy or a previous thyroiditis might be expected. In many nodular colloid goiters sufficient destruction or compression of thyroid tissue may cause myxedema. The toxic exophthalmic type of goiter that runs a prolonged course without surgical interference may gradually cure itself by fibrosis of the thyroid with sufficient destruction of glandular tissue as to permit myxedema. The incidence is five times greater in the female than in the male.

Symptoms and Signs—The symptoms of myxedema are extremely varied and their intensity parallels the lowering of the metabolic rate. The milder cases complain of fatigue, some dryness of the skin with rather frequent

ate compression of the trachea may develop In acute purulent inflammations there is a conspicuous leucocytosis Local applications of heat or cold usually relieve the symptoms, while purulent collections should be drained

Milder forms of acute thyroiditis which sometimes occur with typhoid fever pneumonia etc, subside spontaneously Extensive destruction of the thyroid tissue and resulting fibrosis lead to varying grades of myxedema

Chronic —Chronic thyroiditis may follow an acute inflammation, and is characterized by a diffuse fibrosis As this progresses the consistency of the gland becomes firmer, nodular causing tracheal compression and sometimes involvement of one recurrent laryngeal nerve In proportion to the destruction of the thyroid tissue so hypothyroidism even to myxedema follows

Riedel's struma is a type of chronic thyroiditis which develops insidiously without known pre existing thyroid disease A progressive fibrosis of the gland takes place with pressure symptoms in the later stages Its hardness may lead to the suspicion of carcinoma The surface may be smooth or nodular, and it is usually fixed to the trachea and underlying structures Operative interference is indicated only to relieve pressure as any extensive removal would be followed by myxedema

Tumors of the Thyroid Gland

Benign —Benign tumors of the thyroid gland other than adenoma are unusual Infective granulomatous processes due to syphilis actinomycosis and tuberculosis, occur rarely Adenomas may develop degrees of hyperfunction with toxicity or progress into a true neoplasm A sudden painful enlargement of an adenomatous nodule is due usually to hemorrhage

Malignant —Carcinoma is the commonest malignant growth Sarcoma occurs rarely The *simplex* type of carcinoma is most frequently found and may cause early metastases without penetration of the capsule The Mayo Clinic has stressed the etiologic relationship of the adenoma to carcinoma and on that basis recommends the removal of all adenomas

The diagnosis of an early malignant tumor of the thyroid is difficult It should be suspected in any thyroid enlargement especially if nodular, progressively increasing in size particularly if it is extremely firm or hard With invasion of the capsule fixation to the underlying structures or attachment to the skin follows Metastases take place early principally in the bones lungs and liver Cancer of the thyroid may cause a moderate increase in the basal metabolic rate and paralysis of the vocal cords

Early operation in suspected malignant tumors is imperative The hope *of a cure is poor X ray or radium treatment* should supplement surgical removal Mention has been made above of the use of radioactive iodine in the treatment of thyrotoxicosis The evidence available at present would indicate that it may have a greater use in the treatment of malignant thyroid tumors particularly when metastases have developed The radioactivity is implanted in the thyroid tissues through their specific binding of the iodine Much more careful work remains to be done as unexplained exceptions have been found particularly insofar as different metastases are concerned

enlarged both to the right and the left *The x ray shows a ballooning of the* ventricles but the cardiohepatic angle is acute In many of these cases of apparent cardiac enlargement this is not due to the myocardium but to a pericardial effusion The urine may show considerable albumin with or without granular and hyaline casts and there tends to be a hypercholesterolemia The basal metabolic rate *will range from minus 15 to minus 40 per cent* Altogether the picture is that of an individual mentally dulled and physically slowed up

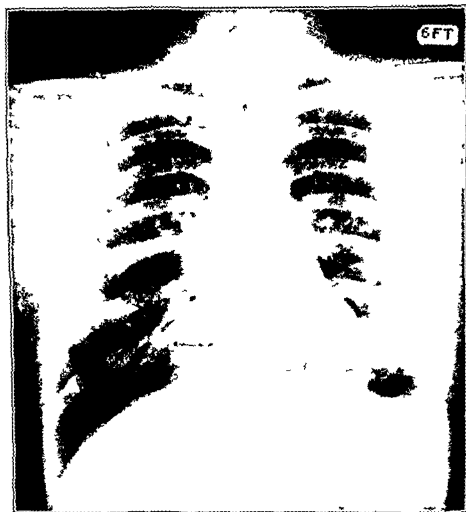


Fig 3[illegible]4—X ray of the chest in the same case as Fig [illegible] after thyroid treatment showing a definite reduction in the size of the heart

Anatomical and Functional Pathology—The thyroid gland in primary myxedema shows *atrophy of the acinar tissue and fibrosis with little round* celled infiltration When a colloid goiter is present the degenerative cysts through pressure destroy much of the functionating tissue

The symptoms in the main are referable to the lowered metabolism which is due to the reduced thyroxin content of the tissue cells The slow pulse and *respiration the mental dullness and physical lethargy* reflect the sluggish

headaches or backaches They may be sensitive to cold, given "to the hot water bottle," and desire extra blankets at night As the basal metabolic rate falls lower (minus 30 to 40 per cent) a marked mental slowing takes place with forgetfulness, and slowness of speech Unusual sleepiness and marked constipation may follow Arthritic pains and muscular stiffness are common

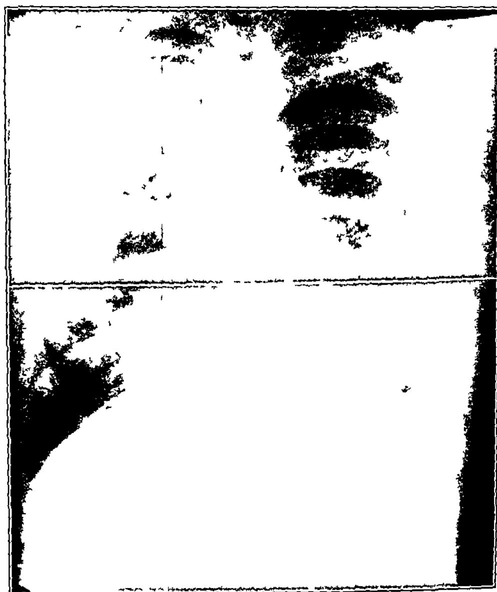


Fig 3 3—X ray of the chest in a case of myxedema showing the cardiac enlargement

Upon physical examination the appearance is important The facial expression has lost its normal animation and become "masklike" with a puffiness about the eyes and neck Some pallor due to anemia is present The skin is dry and may be scaly to a marked degree simulating ichthyosis With this dry skin minor superficial infections are frequently present There is usually a history of a gain in weight The thickened puffy skin will not pit on pressure There is bradycardia 50 to 60 per minute and the respirations may be slowed (8 to 12 per minute) The heart in severe cases is frequently

The iodine content of a thyroid preparation or extract is taken as the index of its biological activity. Although this is not exactly true it is the accepted standard. Different preparations, however, contain differing amounts of iodine. The following example will illustrate this. Burroughs Wellcome produce for use in Canada and Great Britain a thyroid extract which contains 0.3 gm. per cent of iodine according to the B.P. requirement. But they produce for use in the United States a thyroid extract containing 0.2 gm. per cent of iodine (0.17 to 0.23 gm.) to meet the U.S.P. standards. Parke Davis also produces for use in Canada a thyroid extract containing 0.3 gm. per cent of iodine to meet Canadian standards, but this is known in the U.S.A. as "thyroid extract strong" to distinguish it from the standard U.S.P. extract containing 0.2 gm. per cent of iodine. It will therefore be seen that there are two official preparations of thyroid extract used on this continent which vary in strength by 50 per cent iodine content. This is most important in the treatment of myxedema. A careful record of the pulse rate must be kept and at biweekly intervals the basal metabolic rate should be taken. Precordial pain even of a mild degree is a warning that too much work is being thrown upon the heart. Proceed more slowly. It may take three months to bring a severe case back safely to the normal. The maintenance dose in most severe cases of myxedema is approximately gr. 1 per day, but each case must be treated individually according to their needs. A rigid standard for all cases cannot be laid down as the degree of thyroid deficiency is an individual variation and does not necessarily run parallel to the reduction in the basal metabolic rate. It is striking that cases of primary myxedema are much more sensitive to thyroid preparations than cases of secondary hypothyroidism. The latter may tolerate 10 to 20 grains of the same thyroid preparation with an unaltered pulse rate and little effect upon the basal metabolic rate. The explanation for this is not clear. There is little need for altering the maintenance dose after it is once established.

The use of thyroxin intravenously is dangerous. Once administered there is no way of neutralizing its action, which may produce serious or even fatal cardiac effects.

Cretinism

Definition.—Cretinism is a disease referable to defective thyroid function which has its onset in fetal life or infancy. Secondarily other ductless glands may become involved. The disturbance affects both the physical and mental development.

Occurrence.—In the parts of the world where colloid goiter is endemic cretinism is not rare. Such areas are found in Switzerland, the Himalayas and in other regions where the soil is deficient in iodine. Cretinism of this type is spoken of as *endemic*, while a *sporadic* type may develop in early life following some infectious fever. Such cases have no relationship to goiter districts.

Etiology.—Endemic cretinism usually has its onset in fetal life, the mother being deficient in thyroid function. This is closely related to the

tissue inactivity Defective cutaneous circulation leads to the dry skin, inactivity of the sweat glands and susceptibility to infection The skin changes, so characteristic of the disease, are not referable to the lowered metabolism alone This would be suggested by their absence in secondary hypothyroidism and other states with a low metabolism

Diagnosis —Myxedema is one of the diseases frequently undiagnosed in the early stages Studies have shown that five to twenty years may pass from the onset of symptoms until proper treatment is started The conditions with which it is frequently confused are chronic nephritis on account of the urinary findings, arthritis on account of the joint and muscle pains, myocarditis due to the cardiac enlargement and insufficiency, some types of anemia and neurasthenia Since the introduction of the simplified oxygen consumption method for testing the basal metabolic rate, myxedema has been more frequently recognized in its early stages If there is complete absence of thyroid function the basal metabolic rate is minus 40 per cent One must not forget that there are normal people who have a basal metabolic rate as low as minus 15 per cent An exact diagnosis depends upon the presence of the characteristic symptoms and signs associated with a lowered basal metabolic rate Other conditions such as Addison's disease in which a greatly lowered metabolism may be found must be excluded

Complications —Severe myxedema if present for many years leads to degenerative changes in many organs The heart becomes greatly dilated and weakened For a time it was thought that the enlargement was always referable to pericardial effusion The electrocardiogram shows an inverted T wave in lead one with slurring of the QRS complexes This with low voltage suggests the presence of a definite myocardial change These are reversible reactions as when the metabolism is raised to normal, all this electrocardiographic evidence will disappear as the heart returns to its normal condition and size The lowered metabolism is associated with hypercholesteremia which is closely associated with vascular sclerosis and hypertension The chronic albuminuria may be due to anoxemia, and in time with the vascular changes may lead to chronic nephrosclerosis

Treatment —The treatment of myxedema is highly gratifying Its evolution is related to the history of the disease Kocher recognized the myxedematous state following thyroidectomies and termed it *cachexia strumipriva* Grafting of thyroid tissue was attempted, but the graft survived only temporarily In 1891 Murray administered thyroid extract and obtained remarkable improvement

Today thyroid gland extract or the active principle thyroxin is used exclusively in the treatment of myxedema A remarkable mental and physical change occurs as the individual returns to the normal state It is better therapy to change the level of metabolism gradually At the low level the heart and other organs have been doing less work to maintain life Any sudden elevation of metabolism may throw a sufficient strain upon the heart to cause precordial pain, dilatation and sudden death There is more danger of heart failure when definite dilatation has been present before treatment

per day Why the cretin requires such large doses of thyroid is not clear Adults with total myxedema require on an average only 1 grain of the extract for a maintenance dose

Sporadic cretins theoretically should respond better to treatment Unfortunately considerable delay occurs before the true condition is recognized It seems probable that through delay in diagnosis in both endemic and sporadic cases irreparable damage has been effected to the more delicate and highly differentiated tissues

Developmental Anomalies

Since the thyroid is derived embryologically from an invagination and growth downward of the floor of the pharynx one would expect to find developmental anomalies arising from rests of the potential thyroid cells The commonest of these are cysts which occur in the medial line from the root of the tongue to the anterior mediastinum In the latter thyroid rests may develop into large functionating masses of cells which are termed substernal goiters Lingual goiters have been observed located in the deep muscles of the tongue These aberrant thyroid cells are capable of developing states of hyper and hypofunction as in the unusually situated gland

Hypometabolism Without Myxedema

A lowered basal metabolic rate occurs in several diseases without any clinical signs or symptoms of myxedema This should be termed *secondary hypothyroidism* It is characteristically seen in adolescent goiter where the basal metabolic rate frequently ranges from minus 15 to minus 20 per cent Figures of minus 25 per cent have been observed The hypometabolism is due to a deficient production of thyroxin secondary to a defective iodine supply

Low metabolisms are seen in diseases of deficient function of the pituitary adrenal and gonad glands No findings characteristic of myxedema are present In the case of the pituitary and the gonads the normal controlling influence of these glands upon the thyroid would appear to be defective The adrenal raises metabolism both through the effect of adrenalin upon the cells directly and through the stimulating effect of adrenalin upon the thyroid With deficient adrenalin production the basal metabolic rate may fall to a very low figure again without myxedema Levels of minus 48 per cent have been reported lower than is usual with total myxedema

The Thyroid and Pregnancy

At the time of pregnancy an increased call is made upon the thyroid function of the mother This is reflected in a slight physiological fullness of the gland due to increased colloid storage If this enlargement becomes excessive it is a sign that available iodine is lacking and storage of colloid is excessive Pregnant women should be supplied with a normal iodine intake This precaution should be carefully observed in endemic goiter districts Mothers with mild and moderate degrees of myxedema should have the deficiency corrected throughout the whole period of pregnancy In addition to

available iodine in the mother's body. Severely myxedematous women are usually sterile. Sporadic cretinism is really myxedema in a child. The onset takes place in infancy and leads to retardation of physical and mental development.

Pathology.—Most endemic cretins are born with practically no functionating thyroid tissue. An autopsy may reveal a complete absence or a gland that is small, atrophic, or highly fibrous. Sporadic cretins possess a thyroid gland characteristic of the end stages of a chronic thyroiditis.

Symptoms and Signs.—The evidence of cretinism is rarely found at birth. Within a few weeks a suspicion may be aroused by a thickening of the skin and a hoarseness of the cry. The tongue becomes enlarged, and the facial expression may become piglike with the eyes set far apart. At the end of

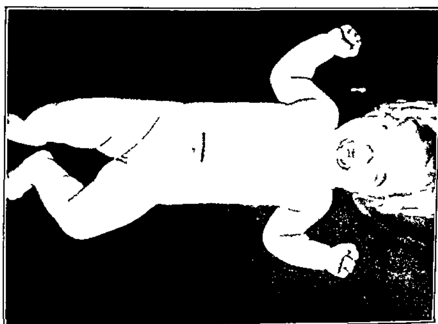


Fig. 3.—Photograph of a cretin aged twenty three months showing characteristic facies, large tongue, atonic muscular state and inability to stand. (Courtesy of Children's Memorial Hospital.)

one year delay in physical and mental development is evident. Dentition is slow and the teeth decay rapidly. There is a pot belly with prominent buttocks and scapular regions. In untreated cases these become increasingly evident as the months pass, and the child may be considered an idiot, although some are clownish and good natured, others seem to be almost like vegetables, sitting for hours in a state of seeming mental abstraction.

Treatment.—Treatment of endemic cretinism is often unsatisfactory. The earlier the diagnosis is made the more hopeful is the outlook. Replacement therapy with thyroid gland or its extract is rational. Unfortunately the basal metabolic rate cannot be used as a guide to dosage but the clinical findings may be relied upon. Talbot suggests ½ grain of thyroid extract per day for infants from four to eight months of age, to be increased to 1 to 2 grains from one to two years and subsequently the dosage should vary from 3 to 6 grains

carbohydrate metabolism more sensitive to the pituitary diabetic hormone (ATF) This however is a matter for further exploration

Whereas the functions of the medulla of the adrenals are comparatively simple in clinical medicine the influences or actions of the adrenal cortex are becoming increasingly diverse and to some extent complicated It is not within the province of this text to deal with all of the probable and indeed possible influences which extracts of the adrenal cortex may have not only on the special physiological processes but upon the structure and even architecture of the body as a whole In fact the time would seem to have arrived when many so called clinical syndromes must be viewed as ultimate complete anatomical organismal breakdowns which are the unusual as compared to the partial deficiencies which in their modified form have a more diverse etiology based upon perverse physiological and psychological impulses

After the pituitary gland the adrenal in our present knowledge is the next most important But even so it is sometimes difficult to be certain as to whether the trains of physiological perversions are primarily situated in one or the other

Therefore it is necessary to find if possible some means or methods to differentiate these complex or at least interwoven functions or clinical patterns Although there are extracts of the cortical adrenal tissue which suggest or even demand attention in their role of therapeutic importance in unsolved systemic diseases the present discussion must be confined to our fairly well established fractions These are

1 The fraction which influences certain electrolytes and water balance or distribution in the body This effect is brought about by the action of the hormone on the reabsorption of these filtrates by the renal tubules If this hormone of the cortex should be absent or deficient sodium chloride and water are lost in the urine while potassium is retained in excess It is obvious from such an imbalance of control that there will be a serious sodium chloride depletion and dehydration with hemoconcentration and potassium intoxication

2 There has now been determined a cortical hormonal function which influences the carbohydrate protein and fat metabolism of the body in general It is well known that during periods of starvation the glycogen stores in the liver and muscles are replaced and maintained by the conversion of glucose and glycogen from body proteins This is apparently brought about by the action of an adrenal cortical hormone When this is deficient or absent this function may be impaired or indeed almost completely absent Therefore periods of relative hypoglycemia may occur In fact the blood levels may be so reduced as to produce severe symptoms or even threaten life

3 In the classical description by Addison the presence of a brownish pigmentation of the skin and mucous membranes was one of the prominent features In fact today its presence is considered most important in the diagnosis of the complete syndrome and therefore has an important bearing upon the eventual prognosis The pigmentation is due to increased deposits of melanin The reason for this deposition is not known It cannot be attributed to any recognizable hormone fraction of the adrenal cortex But this is not surprising as the number of these fractions is being continually increased but in such man

the thyroid gland or extract required, small daily doses of iodine are advisable Such care of the expectant mother will materially reduce the incidence of thyroid deficient infants

DISEASES OF THE SUPRARENAL GLANDS

Introduction

Although the suprarenal glands were known to exist in 1563 (Eustachius), no conception of their function was held until Thomas Addison, in 1855, described the clinical aspects of the disease which now bears his name Shortly Vulpian who discovered the chromaffin system, demonstrated the presence in the suprarenals of a substance which turned greenish on contact with ferric chloride (probably adrenalin) The vasoconstrictive action of medullary extracts was studied by Oliver and Schaefer and Takamine and Aldrich isolated the adrenalin base in crystalline form In 1904 the chemical composition of adrenalin was determined by Jowett, and Stokes accomplished its synthesis The function of the adrenal cortex was unknown until Rogoff and Stewart as well as Hartman prepared an aqueous extract with physiological action Swingle and Pfiffner showed that the physiological action could be greatly enhanced by lipoid extraction

The suprarenal glands are two in number, one resting at the upper pole of each kidney in the retroperitoneal fat They are composed of a cortex and a medulla The cortex is made up of epithelial cells having their origin from the genital ridge The medulla is composed of chromaffin cells arising from the embryonic sympathetic nervous system The cortical cells have the same origin as the interstitial cells of the testes

The exploration of the functions of the adrenal glands has expanded conspicuously in recent years It is conceded that the medulla and the cortex have unrelated embryonic origins and as would be supposed essentially different functions

The medullary cells have according to our present knowledge only one function namely the production of adrenalin (epinephrin) This has a strong vasoconstrictor effect on the peripheral arteries but has a dilating action on the coronary arteries and the bronchial musculature As a consequence of general arteriolar vasoconstriction the systemic blood pressure is raised If the therapeutic amounts administered are large there is consequent pallor due to vasoconstriction of the skin arterioles with palpitation of the heart This however should be a relatively unusual occurrence but when spontaneous it is strongly suggestive of the presence of a paraganglioma (see page 943)

The effect of adrenalin on the bronchial musculature is one of the most spectacular in clinical medicine This is amply demonstrated in uncomplicated bronchial asthma where relief may be obtained in a matter of minutes

Adrenalin has in addition certain other effects It can produce hyperglycemia and glycosuria through release of glycogen from the liver In this way it is an apparent antagonist to insulin This is supposed to be effective through stimulation of the sympathetic nervous system This might with justice be questioned and an alternative suggestion be offered that it renders

Hyposuprarenal Function

The Exhaustion Syndrome (Hypoadrenalemia).—The adrenal glands are capable of maintaining life in the presence of unusual strain or stress. Under conditions detrimental to life there is normally an hypertrophy of the glands. If this hypertrophy with increased function fails to occur, a state of relative adrenal insufficiency may develop. This is termed "the exhaustion syndrome" and is due to absolute or relative hypoadrenalemia.

Symptoms.—The symptoms characterizing the syndrome are chronic fatigue, exhaustion, low blood pressure and in some cases a lowering of the plasma sodium with dehydration. The basal metabolic rate is usually normal *or slightly depressed.*

In doubtful cases evidence can be obtained by giving a low salt diet, not more than one gram a day. If there is adrenal insufficiency this will cause a moderate blood concentration (hemoglobin elevated) and a negative sodium balance. In more severe cases a fall in the blood sodium and an increase in potassium will follow.

Treatment.—Treatment consists in giving salt, 10 to 15 grams per day, adrenal cortical extract and a liberal intake of water.

Acute Insufficiency of the Adrenal Cortical Function (Waterhouse-Friderichsen Syndrome)

There occurs occasionally in severe infections with a bacteriemia, particularly due to the staphylococcus or the meningococcus, a severe and precipitous collapse which closely simulates an Addisonian adrenal crisis. In these cases there is usually an hemorrhagic component. Such is not different from a similar state as classically described in many infectious diseases, hence the term "black" scarlet fever, measles, smallpox, etc. But it is well known that the two infections mentioned above have proverbially associated hemorrhagic lesions and it is to be expected that the adrenals may share in this process. It is significant, however, that in the great majority of such cases coming to autopsy the lesion is bilateral.

There is another aspect of this syndrome which does not coincide with the above infections, namely its frequency in the causes of death in the newborn. As yet any definite connection between the above mentioned infections and its occurrence in these cases has not been established. But the fact remains that it should always be suspected when the clinical syndrome as described below occurs in cases with a severe bacteriemia or in newborn infants.

Symptoms and Signs.—As suggested above, the outstanding features are the unexpected appearance of the symptoms and signs of *profound shock* with all the evidence, if sought, of complete adrenal insufficiency. Indicative of the severity of the process is hyperpyrexia. The occurrence of unexplained cyanosis, *falling blood pressure, tachycardia, rapid and shallow breathing,* mental confusion to semi- or complete coma are not particularly unusual in overwhelming infections, but to meet the criteria of this syndrome there must be presented some laboratory evidence *of acute adrenal deficiency,* such as a definite hypoglycemia, a profound sodium and chloride loss, a conspicuous in-

imal amounts that experimental progress is handicapped, and furthermore, there are undoubtedly other fractions which remain to be recognized and amongst these is this elusive one which controls or at least determines the degree of melanin metabolism

4 The influence of the adrenal cortex upon genital development in both the male and the female is most intriguing It is now well accepted that virilism and/or the so called Cushing's syndrome may be produced by hyperfunction of the adrenal cortex without demonstrable lesions of the pituitary gland On the contrary evidence of hypofunction of the sex glands may also result from adrenal insufficiency as in the complete syndrome of Addison's disease

It must not be conceived that disease of the adrenals always leads to the complete clinical feature of Addison's disease As in diseases of other ductless glands there is often a quantitative modification of the whole function of the gland or any part thereof This is emphatically emphasized in both the quantitative and qualitative physiological potency of cortical hormone preparations Although this may be intriguing to the sterol chemist it is a perpetual source of aggravation to the clinician both in diagnosis and treatment The clinical patterns of adrenal cortical function are just as quantitative as are those of the pituitary gland and it helps him but little at the moment to know that corticosterone with an oxygen atom at the C_3 C_{11} C_{20} and C_{21} positions make it operative in regulating mineral and carbohydrate metabolism while removal of C_{11} oxygen atom increases sodium and chloride retention but busts wide open carbohydrate metabolism while the addition of an oxygen atom at C_{17} (17 desoxycorticosterone) produces practically an opposite effect But in time and with further critical clinical study these seemingly complex patterns will be elucidated and simplified both as to diagnosis and specific therapy

Verzar has shown that in the adrenalectomized state there is a marked delay of absorption of glucose and fat from the intestinal tract This delay is considered to be due to a failure of phosphorylation of glucose and fat in the intestinal mucosa This failure of phosphorylation would appear to be due to the absence of cortin which is probably flavin phosphate and identical with vitamin B In the absence of cortin adrenalectomized animals can be kept alive with flavin phosphate but not with lacto flavin This observation may be a fundamental one and if further investigated may throw some light upon the disturbed metabolism in cases of adrenal insufficiency It may also lead to a clearer understanding of failure of fat absorption in other diseased states (See page 639)

The suprarenal glands do not function independently of the other ductless glands The anterior lobe of the pituitary gland secretes a hormone termed its adrenotropic factor which stimulates the cortex of the suprarenal Removal of the pituitary results in atrophy of the suprarenal cortex This is well shown in Simmonds disease Long has shown that complete adrenalectomy in a depancreatized animal will lessen the severity of the diabetic state and that if the animals do not eat they will die in hypoglycemia In the main all substances injurious to the body tend to cause the adrenal to enlarge J C M

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crease in the blood serum potassium, and clear evidence of pronounced hemo concentration by the hematocrit It is upon such evidence that a *factual diagnosis* may be made, which however, is only occasionally possible On the other hand a speculative diagnosis of such can do no harm, and the therapy indicated, whether the diagnosis is specifically demonstrated or not, is in the way of wisdom

Treatment—The treatment is a matter of common sense The infection must be combated by all means in our power, by sulfonamides, penicillin strep tomycin etc One cannot tarry in determining the specific agent responsible Time may reveal this The hemoconcentration and dehydration must be com bated by the infusion with plasma glucose and hypertonic sodium chloride solutions This in its essence is acute substitution therapy and massive in jections of aqueous adrenal cortical extracts of hopeful potency should be continued until the acute condition has been surmounted Too much can sel dom be given but it should never be held to be too little and too late There is one word of caution however excessive doses of desoxycorticosterone acetate may produce fatal results through producing cardiac distention and pulmonary edema by drastic and acute increase of the blood volume

There is still one aspect of this syndrome to be settled If patients re cover from this acute and almost catastrophic condition why do they not develop the classical syndrome of Addison's disease? This query is particu larly directed to the supposed cases of recovery in the newborn

Addison s Disease

Definition—Addison's disease is a deficiency of the cortex and medulla of both adrenal glands

Etiology—Older autopsy series show tuberculosis of the gland to be the primary cause in about 80 per cent of the cases With recent studies and improvement in diagnosis atrophy and aplasias are now accounting for fully 50 per cent of the deaths tuberculosis comes second and syphilis third

Anatomical and Functional Pathology—The anatomical lesions found at death in the adrenal glands are atrophy aplasia tuberculosis or syphilis The atrophic gland is small (normal 4 to 10 grams) and characteristically shows a small round cell infiltration The atrophy involves both cortex and medulla, and is bilateral Small round cell infiltration takes place in other organs especially the liver Aplasia may be bilateral or unilateral If unilateral, the other gland may show marked atrophy Tuberculosis when present is bilat eral and causes extensive destruction of the gland by a fibrocaseous process Necrosis may be small and patchy, but again the gland may be a necrotic mass enclosed in a fibrous capsule The tuberculous lesions involve both medulla and cortex, and calcification as demonstrated by x ray is not unusual The caseous masses are usually large weighing from 20 to 30 grams

With atrophy or destruction of the adrenal glands a marked interference with their function follows The cortical hormone controls the passage of sodium between the blood plasma and the tissue cell If it is deficient the sodium tends to pass from the blood into the tissues As it passes into the kidney cells it is lost to the body via the urine Water follows sodium, with a

resulting dehydration and blood concentration The failure of phosphorylation of glucose and fat in the intestinal mucosa with their impaired absorption has a causal relationship to the asthenia undernutrition and low glycogen reserve There is also a low blood pressure hypoglycemia and a lowered oxygen consumption These may result directly through deficient cortical function or indirectly by this lack upon other organs

Symptoms and Signs — The onset of the disease is usually insidious Progressive weakness, asthenia and dizziness upon a change of posture are among the earlier symptoms The cardiac shadow by x ray is small (see Fig 356) and resembles that remarked upon in pulmonary tuberculosis (see page 304) Pigmentation of the skin and mucous membranes due to melanin may occur early but is not necessarily present As the disease progresses gastrointestinal symptoms may be conspicuous Nausea with irregular vomiting, diarrhea, and a gassy indigestion are prominent In its later stages crises with collapse severe dehydration hypoglycemia and marked hypotension precede death

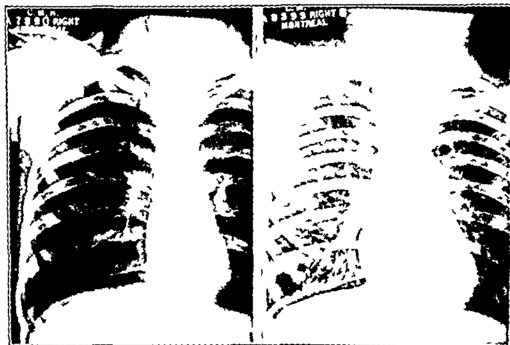


Fig 356   Fig 357

Fig 356 —X ray of the chest of a a of Addison s disease in a crisis Note the small tear drop heart

Fig 357 —X ray of the chest of the same case as in Fig 356 during treatment with sodium chloride Note the change in the size of the heart

Addison s disease offers a multiplicity of abnormal laboratory findings The urine volume is decreased and concentrated, the urine contains creatin The blood nonprotein nitrogen and urea are raised, a result of impaired renal function The basal metabolic rate is usually low even to minus 48 per cent Achlorhydria s present The severer cases show a lowering of the blood sodium with evidence of blood concentration In crises the blood volume is

crease in the blood serum potassium, and clear evidence of pronounced hemo concentration by the hematocrit It is upon such evidence that a *factual diagnosis* may be made which however, is only occasionally possible On the other hand a speculative diagnosis of such can do no harm, and the therapy indicated whether the diagnosis is specifically demonstrated or not is in the way of wisdom

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their excretion is below the normal level the less will be the probable adrenal cortical activity It must however be borne in mind that pituitary deficiency may lead to a similar reduction of their excretion

(b) If the diagnosis is in doubt it may be directly clarified by the administration of the adrenotropic hormone of the pituitary If the response is favorable it indicates that the adrenal cortex is active and that the primary deficiency is in the former gland

2 *Indirect Methods*—

(a) Patients with adrenocortical insufficiency are extremely sensitive to insulin Therefore a cautiously administered and controlled test as to this may be carried out But it must always be borne in mind that there are other conditions in which increased sensitivity to insulin may be present These are chronic diffuse hepatic disease adenoma of the islands of Langerhans and pituitary gland deficiency A somewhat similar test may be effected by placing the patient on a low carbohydrate diet with an anticipation of an aggravation of symptoms

(b) The sensitivity of a patient to a low salt (sodium chloride) intake may also be used as an indirect diagnostic procedure A somewhat analogous test is based upon the disturbed kidney function to maintain a proper water balance The Kepler Lower water test is based upon the abnormality The patient voids at 10 P M and all urine is collected and measured to 7 A M If there is adrenocortical insufficiency there will be an excess water loss during this time which will be demonstrated by a retention of water if the patient be given an adequate amount (20 c c per kilo of body weight) rapidly by mouth If any hourly amount of urine passed during the next four hours exceeds the night volume it indicates that there has not been an excessive water loss during the night and therefore Addison s disease may be excluded If the contrary occurs this disease must be considered as possible

These indirect tests are fraught with danger and should be undertaken only in the hospital where constant vigilance is possible as they may precipitate an Addisonian crisis This particularly applies to the first three

Complications—An infection however mild is a serious complication in Addison s disease The body fails to react either by a rise in temperature or by leucocytosis Unless the greatest care is taken to maintain the glycogen reserve the patient may die in hypoglycemia This is most common during convalescence about eight to twelve days after the onset of the infection

Prognosis—The prognosis is determined in part by the basic nature of the disturbance Tuberculosis of the adrenals is always fatal With specific treatment syphilis of the adrenals should improve In Addison s disease due to atrophy of the glands life can be greatly extended by the use of a cortical extract and salt In all types of Addison s disease cortical extract and salt will improve the general health of the patients provided they maintain an adequate caloric diet Their future depends greatly upon the maintenance of a glycogen

greatly reduced Death is often sudden, and is preceded by a precipitant fall in the blood sugar Increase of the blood potassium is of great significance

It will be apparent from the account of the adrenal hormones outlined above and the concept that all functions of these may not necessarily be equally deficient that the pattern of Addison's disease may vary in detail in different patients Also it has been found that these variations may not always run true to type in recurrent exacerbations in the same case In some cases abnormal pigmentation may be much more prominent and persistent than in others also a profound impairment of the carbohydrate and protein metabolism may be the outstanding feature while at other times the electrolyte and water imbalance dominate the clinical picture It is true that the latter two may be fairly consistent causes of the Addisonian crises in any given case, but this is not without exceptions and one should always be alert for these exceptions as their appreciation in successful therapy cannot be overemphasized

It has been mentioned above how the different functions of the adrenals may be deficient both independently and collectively Therefore it is important at any one time to determine which one or ones may be principally at fault The abnormalities of pigmentation have no effect per se upon the well being or life of the patient but only serve as an indication of the possible primary disturbance Likewise is the effect on the gonads This may be inconvenient but does not menace life Here again it may act as a signpost

Diagnosis —The typical case of Addison's disease shows progressive weakness with hypotension and a small heart (see Fig 356) Gastrointestinal intolerance and pigmentation of the skin and buccal mucosa are present If these findings occur associated with tuberculosis in some organ, a strong suspicion of Addison's disease is justified

The laboratory examinations that will support the diagnosis are a low serum sodium (310 or less mg per cent), a lowered basal metabolism (minus 20 to minus 48 per cent), evidence of impaired renal function (nonprotein nitrogen and urea moderately raised) creatinuria achlorhydria, oliguria, and a negative nitrogen balance The blood sugar will be at the lower level of normal (70 to 80 mg per cent) In crises the serum sodium will drop, dehydration become more marked as evidenced by concentration of the blood and hypoglycemia of a severe degree may occur A biopsy of the pigmented area of the skin will show its increased melanin content and tuberculous cases sometimes have calcified adrenals as demonstrated by x ray

Diseases that result in a dark pigmentation of the skin offer most chance for error in diagnosis Metallic poisonings especially silver, might be confusing Hemochromatosis pigmentation occurs with glycosuria and an enlarged liver Sections of the skin show an excess hemosiderin Tuberculous and other peritoneal lesions may also exhibit cutaneous and mucous membrane pigmentation, as may also hyperthyroidism, idiopathic steatorrhea and pellagra

There are however certain direct and indirect methods available for the evaluation of the adrenocortical functions

1 *Direct Methods* —

(a) The urinary assays of the 17 ketosteroids and of corticoids may afford valuable information as to the cortical activity The more

to control the symptoms If the serum sodium can be successfully elevated by salt less cortical extract will be required Also the present standardization of the cortical extract is being carried out upon adrenalectomized rats and dogs, with little account being taken of the serum sodium level of the animals In the near future no doubt these refinements will be more rigid, and gross variations in potency eliminated Ordinarily a dose of 2 to 4 c c a day (1 c c containing the physiologically active fraction from 40 grams of fresh adrenal gland) is required



F 4 Ph t raph f n 35 ll with Addison's disease Note pigmentation of f neck and n l l w m B P 88/58 blood odium 31 ng per cent

The primary effect of the cortical extract is to raise the serum sodium by withdrawing it from the tissues including the kidney cells This results in less sodium being lost in the urine Sodium chloride administered in 10 to 20

reserve in the liver Before the use of a cortical extract cases of Addison's disease died in dehydration with marked hypotension The blood sugar was low but not sufficiently depressed to be dangerous Since a physiologically active cortical extract has been available, and the importance of salt has been appreciated, death has occurred most frequently from hypoglycemia precipitated by infection There has been no evidence of dehydration

Treatment—The treatment of Addison's disease consists of three phases (1) measures to improve the general health and to combat the development of infections, (2) the more specific treatment of the defective cortical and medullary functions, and (3) the treatment of the basic specific infections tuberculosis or syphilis, if present

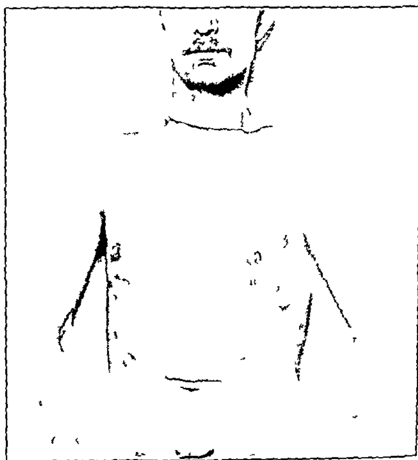


Fig 358—Photograph of a case of Addison's disease showing the diffuse pigmentation of the neck and body At autopsy complete destruction of both suprarenal glands by tuberculosis was found

The patient with Addison's disease is now a semi invalid, so fresh air and sunlight should be encouraged Avoidance of cold and no more than mild physical activity should be insisted upon Systematic rest periods and a diet high in carbohydrate to maintain a good glycogen reserve are important Several small frequent meals are best tolerated

The adrenal insufficiency should be treated by a standardized cortical extract and salt The dosage of the cortical extract will depend upon the level of the serum sodium The lower it is, the more cortical extract is necessary

to control the symptoms If the serum sodium can be successfully elevated by salt less cortical extract will be required Also the present standardization of the cortical extract is being carried out upon adrenalectomized rats and dogs, with little account being taken of the serum sodium level of the animals In the near future no doubt these refinements will be more rigid and gross variations in potency eliminated Ordinarily a dose of 2 to 4 c c a day (1 c c containing the physiologically active fraction from 40 grams of fresh adrenal gland) is required



Fig 3 9—Photograph of woman, 38 years old with Addison's disease Note pigmentation of face neck, hands and lower arms B M R –8 blood sodium 315 mg per cent

The primary effect of the cortical extract is to raise the serum sodium by withdrawing it from the tissues including the kidney cells This results in less sodium being lost in the urine *Sodium chloride* administered in 10 to 20

gram doses per day can be given in capsules of 0 5 gram each This will help to raise the plasma sodium A marked improvement in the well being of the patient will take place with such treatment Weakness improves, hunger replaces nausea and vomiting, there may be a gain in weight with some decrease of pigmentation The basal metabolic rate may rise, renal function improves, correcting the urea retention but a rise of blood pressure may not be outstanding If hypotension is marked it may be improved slightly but does not return to a normal level There is a conspicuous increase in the cardiac shadow by x ray (see Fig 357) Wilder has found that the best results are obtained with a low potassium diet Vitamin B_2 should also be given in full dosage Desoxycorticosterone acetate has some of the physiological activities of cortin such as increasing blood pressure, reducing blood potassium raising blood sodium etc It does not affect the hypoglycemic crises It may be administered intramuscularly or sterile tablets may be inserted into the muscles and produce an effect lasting for months Sometimes the potassium may be reduced to levels dangerous to the nervous system It is, therefore most important that the requirements for desoxycorticosterone be carefully estimated before implantation as in addition to the low potassium effects on the nervous system the blood volume may be increased to a dangerous amount and acute cardiac failure may result The same may occur with uncontrolled intramuscular injections

In the urgency of collapse large doses of cortical extract, 10 to 20 c c (5 to 10 times the ordinary dose) should be given intravenously and repeated at four to six hour intervals if necessary Hypertonic salt (5 per cent solution) and 10 per cent glucose in amounts of 200 to 300 c c intravenously should be beneficial If the serum sodium can be maintained close to the normal level (normal 330 to 340 mg per cent) dehydration will correct itself Until that can be accomplished fluids should be given freely and in crises intravenously As soon as possible frequent carbohydrate feedings should be given to help combat hypoglycemia

Treatment of tuberculosis, if present, should be conducted along the lines recognized as suitable and syphilis if present, should be treated in a conservative manner

Hypersuprarenal Function

Cortex—Cortical tumors are associated with hyperfunction of the suprarenal cortex These lesions will be described under Tumors

Medulla—States of excessive adrenalin output occur As Cannon has shown the emotions fear anger etc cause an increased adrenalin discharge which raises the blood sugar and makes energy rapidly available to meet the emergency Mild repeated insults will cause an hypertrophy of the adrenal glands with excess adrenalin discharge More severe insults if continued, will not result in adrenal hypertrophy and a degree of adrenal insufficiency may follow (exhaustion syndrome)

Tumors

Tumors of the suprarenal gland may arise from both the cells of the cortex and those of the medulla It will be remembered that the cells of the

cortex and the medulla have a different embryological origin and accordingly tumors arising from these cells would be expected to produce different results

Tumors of the Cortex

Cortical tumors are composed of the epithelial cells characteristic of the cortex Presumably the cells of the tumor have the same function as those of the normal gland Thus we are dealing with a state of hyperfunction of the cortical cells As yet no clinical entity has been described as being associated with an excess of hormone from a normal adrenal cortex

According to the period in life at which this increased physiological action occurs, so different manifestations of the syndrome develop In fetal life the cortical activity leads to congenital pseudohermaphroditism in infancy to pubertas precox and in adult life to virilism and hirsutism

It may be convenient to classify these developments as follows

1 Adrenogenital —
 (a) Pseudohermaphroditism
 (b) Pubertas precox
 (c) Virilism
2 Adrenometabolic —
 Cushing s syndrome
3 Mixed types

Pseudohermaphroditism may develop in both the male and the female but it is much commoner in the female In the male there is the tendency to homosexuality In the female the findings suggest a reversion to the male type enlargement of the clitoris to the size of a small penis with failure of development of the uterus and ovaries

Precocious puberty (pubertas precox) occurs before puberty and usually in a young child It is more common in the male It is characterized by an adult development of the secondary sexual characteristics as well as the sex organs themselves The penis and testicles grow to adult size the voice is low pitched the pubic hair becomes abundant with the distribution of the adult male In addition there may be excess growth of hair over the chest back arms and legs Pubertas precox developing in the female child causes hypertrophy of the clitoris with excess growth of pubic hair, tending to revert to the male type in its distribution

If the cortical tumor develops after mature development has taken place the findings are not so striking There is a tendency both in the male and the female to become more masculine This is usually described under the general term of *virilism* The male may develop a greater growth of body hair of a coarse texture with a tendency for the skin to become thicker although cases have been reported of gynecomastia and feminism in the male The female reverts to the male type enlargement of the clitoris atrophy of the breasts uterus and ovaries with the pubic hair of male distribution and a deep voice A beard may develop and the skin become coarse

Mention has been made on page 897 to the occurrence of Cushing s syndrome in lesions of the adrenal cortex Many of the features described under

this heading have a similarity to those in the adrenogenital group But there is one striking difference namely, the hyperglycemia which does not occur in the first group This would indicate that the metabolic function of the adrenal was stimulated by some abnormal secretion As this same syndrome may occur with a basophilic adenoma of the pituitary, certain thymomas and arrhenoblastomas, there is a strong suggestion that, although as mentioned above no definite clinical syndrome has been identified with an excessive production of normal adrenal cortical hormone, there may be other cortical fractions which are as yet unknown or at least unrecognized as being able to produce these clinical patterns

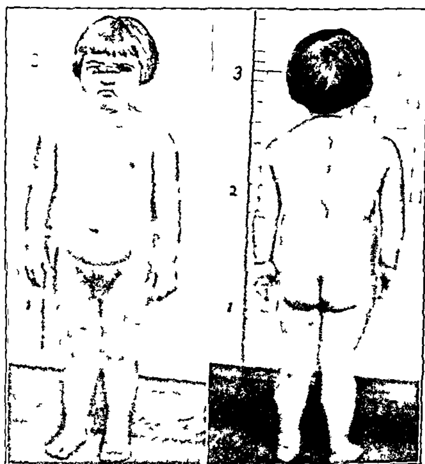


Fig 360 Fig 361

Fig 360 —Front view of a female child aged four and a half years with adrenal cortex tumor Note hirsutism and precocious puberty (Courtesy of Dr Hector Mortimer)
Fig 361 —Back view of the same patient showing virile-like arrangement of the hair and overdevelopment of the shoulder girdle (Courtesy of Dr Hector Mortimer)

Diagnosis —The diagnosis of this condition is sometimes one of some difficulty for a number of reasons The clinical pattern may be incomplete or there may be a mixed pattern with some of the features of the adrenogenital and the adrenometabolic groups If a tumor is palpable in the loin or even if a tumor may be demonstrated by x-rays after perirenal insufflation which should be carried out with the greatest caution and by experts and then as a last resort, the cause is fairly clear It must be appreciated that these syndromes

may be associated with adrenal cortical hypertrophy alone without tumor formation Furthermore somewhat similar syndromes have been found associated with tumors of the pituitary thymus ovaries and gonads but in the adrenogenital group the precocious puberty is not complete as menstruation does not occur in girls nor spermatogenesis or priapism in boys which is contrary to the precocity of pituitary and genital tumors Endocrine assays may be helpful not so much in definitely pointing to the adrenal cortex as to lesions of other glands

Treatment—The treatment of these cases depends upon the demonstrated presence of a tumor If one is present its removal is indicated if metastases have not occurred Some even advise exploratory operation in any case Prior to our knowledge of the physiological action of the suprarenal cortex their removal was usually followed by collapse and death However the literature contains an increasing number of cases where successful removal has been accomplished

The cause of death following their removal is hypoglycemia This is due to the fact that the other adrenal is usually atrophic With the aid of an active cortical extract and salt the postoperative mortality should be much lower in the future

Tumors of the Medulla

There are three types of medullary tumors neuroblastomata ganglioneuromata and paragangliomata or pheochromocytomata The neuroblastoma arises from the most embryonic type of cell and the paraganglioma from the mature chromaffin cell The neuroblastomata have early metastases and run a malignant course The paragangliomas are not so malignant and have been successfully removed

Paraganglioma

Of the medullary tumors the only one which produces a clinical pattern is the paraganglioma It has been found almost equally in both sexes it is more common on the right side but may be bilateral As a rule they are small but they may attain sufficient size to be palpable or even to impinge upon neighboring organs They usually are benign but a few cases have been reported which were malignant either systemically or locally invasive

The clinical pattern of hyperfunction of the adrenal medulla caused by paraganglioma is that to be expected from an excessive dosage of adrenalin It is as follows (a) conspicuous hypertension (200 to 300 mm Hg) pallor palpitation precordial oppression and throbbing headache (b) apprehension blurring of vision uncontrollable tremor dilated pupils and hyperpnea (c) hyperglycemia and glycosuria As might be expected all of these findings may vary from time to time in intensity Further although it is most distinctive for attacks to be paroxysmal the hypertension and certain of the other symptoms and signs may be persistent and continuous and may lead to confusion in the diagnosis of essential hypertension It should always be given consideration in the diagnosis of the latter Some patients may associate attacks with certain movements or articles of clothing such as a tight

girdle or belt bending to the right or left from the waist This may be reproduced by deep palpation in one or the other or both loins However the absence of these should not be exclusive

Diagnosis—The diagnosis of paraganglioma of the adrenal depends upon the recognition of the total syndrome over a period of time and the reproduction of attacks if possible Perirenal insufflation with x ray examination is not advisable as the tumors are usually small and the dangers are excessive

Prognosis—This rests upon two aspects If the presence of such a tumor is not recognized there will develop in time all the vascular and organismal changes of structure and function associated with severe hypertension The other important feature is the danger of collapse occurring during and after operation from acute adrenalin deficiency and the possibility of an associated acute adrenal cortical crisis

Treatment—Removal of the tumor or tumors is likely to be a specific cure It must be appreciated that these tumors may be multiple and further, that metastases may have occurred If so, a cure cannot be expected

The patient should be carefully prepared for operation as if in expectation of an adrenal cortical crisis (see page 940) A sudden fall of blood pressure at operation or immediately following would probably indicate an acute adrenalin deficiency which could be countered by intravenous administration of adrenalin either by repeated injection or by the drip method (see page 1450) Adrenalin in oil intramuscularly is of value for its prolonged action in the days following operation There should be constant vigilance to detect any evidence of cortical deficiency such as severe hypoglycemia rapid sodium and chloride loss severe dehydration and persistent gastric disturbances These should be treated as in an adrenal cortical crisis

DISEASES OF THE GONADS

Introduction

It will have been apparent in the foregoing sections of this chapter that there is an intimate correlation between the functions of the different ductless glands Each one may have what appears on first sight to be a primary purpose but yet when viewed from a broader angle they all conspire toward playing their part in preserving two biological fundamentals namely self preservation and propagation The primary purpose of the gonads is the latter, but they are influenced in this function by the others It would be as impossible to consider the variable functions of the pituitary suprarenal thyroid, thymus and pineal glands without being impressed by their occasional and often spectacular influence on gonadal function as to view growth, nutrition, the strength to resist physical and environmental changes and the battle for the preservation of life without appreciating their dominating power to help preserve the species All physiological processes are coordinated to make this preservation as certain as possible considering the vicissitudes to which the species is exposed The intermingling of preservation and propagation are relatively indivisible although they may appear unconnected in a casual

survey The race may not always be to the strong but it undoubtedly is to the fecund, given proper environment It has already been emphasized that although the endocrine organs have a profound influence upon the character and capacity of the body, they are also sensitive to gross abnormalities of the internal and external environment The gonads are no exception to these influences Therefore, in considering the diseases of the gonads it is necessary to take into account the function of the other endocrine glands the quality and quantity of the diet and the presence of infections or chronic visceral diseases

It may be stated with certainty that in addition to spermatogenesis and ovulation there are in the male and female incretions or hormones which determine the development of the secondary sex characteristics and in the female prepare the uterus for gestation It is possible to have normal sex characteristics and sex organ development without normal fertility The mysteries underlying propagation both in the male and the female are as much biochemical as anatomical and are only beginning to be understood Such advances as have been made are viewed by the best and most conservative authorities as an earnest of the future They are hesitant to be dogmatic or even slightly positive but this has not prevented many whose knowledge of the fundamental and experimental difficulties is to say the least fragmentary, from postulating upon clinical problems with a certainty which is almost apocryphal There are so many factors influencing sexual development and function that it is sometimes difficult to unravel the tangled skein Under diseases of other ductless glands such as adrenal and pineal glands reference is made to their influence in producing abnormalities in sexual development A sharp distinction must be appreciated between the development of these and an excessive libido The latter is more dependent upon psychic stimulation than upon anatomical characteristics although unless these are fairly normal propagation may not be accomplished It is true that there may be excessive sexual activity in the male and female without there being any demonstrable anatomical abnormality

Before proceeding further it would be well to review briefly the important facts which are now fairly well known regarding the internal secretions of the gonads For this purpose it seems reasonable to separate the male and the female incretions In the period of childhood the progression is ordinarily without any spectacular developments but from the age of about eleven onward a differentiation between sexes occurs This is so well known by the adult laity and even appreciated by the children themselves that it would seem superfluous to recount it here However for the matter of comparison this seems necessary

Puberty—The boy loses his baby fat develops more muscle hair begins to appear on the pubis in the axillae on the chest and chin and eventually assumes the masculine distribution the penis scrotum testicles prostate seminal vesicles and epididymis enlarge and there is often a rapid skeletal growth with broadening of the shoulders narrow pelvis and proportional lengthening of the long bones in relation to stature and a striking change in

girdle or belt, bending to the right or left from the waist This may be reproduced by deep palpation in one or the other or both loins However the absence of these should not be exclusive

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period when the deficiency occurs This is particularly evident in regard to the skeletal and sexual development cutaneous attributes etc These may be outlined as follows

A If it occurs before puberty one might expect

(1) Anatomical features At puberty the extremities continue to grow in comparison to the size of the trunk as the ossification centers are delayed in closing

(2) The trunk as shown by the shoulders is narrow but the pelvis may be relatively broad simulating the female contour which may be accentuated by a certain degree of genu valgum

(3) The voice remains childish due to arrest of laryngeal development

(4) The secondary sex characteristics do not develop and this includes the absence of hair in the usual masculine distribution in fact this usually remains juvenile with absence over the pubis and in the axillae with very scanty hair on the face chest abdomen arms and lip It may resemble in this respect the most feminine of women

(5) It would be expected that the genitals would remain childlike to outward appearances Also the prostate does not develop nor do the testicles and epididymides

(6) Although there may be a certain degree of obesity as in Frohlich's syndrome this by no means necessarily occurs Parallel to this there may be an apparent gynecomastia but this is not real and only occurs in those cases with obesity

B If hypogonadism is initiated after puberty the pattern is usually entirely different

(1) The skeletal features do not occur and the patient to all intents and purposes remains as he is

(2) The voice may lose some of its robustness and a bass singer may become a baritone or even a tenor

(3) The secondary sex characteristics may become less masculine such as a decrease in beard axillary and pubic hair and a reduction in muscular activity and stamina But it is not to be expected that they lose ambition intellectual drive and accomplishment In fact many seem to divert their energies into quite productive avenues of endeavor This however does not exclude the possibility of a psychoneurotic pattern due to a sense of inferiority and sexual frustration Most probably this feature is analogous to the biological finality so often associated with the female menopause

(4) The testicles and prostate usually become smaller and the victim impotent but libido remains as this is a psychogenic function

Causes of Hypogonadism—It must be appreciated that hypogonadism may be a matter of degree ranging from a slight deficiency to a complete loss of function It is important to bear this in mind not only in the diagnosis but also in the prognosis and the expectations of successful therapy

(1) *Primary Causes*—These rest in the testes themselves and may be congenital or developmental on the one hand or traumatic or infectious on the other Primary congenital cases in which there is a testicular defect at birth

the voice due to alteration of the larynx These are everyday occurrences and should not be belabored except in so far as they may not progress in a reasonably ordered manner

In the female other distinctive changes occur in a normal fashion The breasts develop the nipples become more erectile, the pubic and axillary hair appear the labia become more prominent and differentiated the pelvis broadens and there is a rounded accumulation of panniculus over the pelvis thighs abdomen and shoulders so well painted by the classical artists The final culmination of this biological evolution is the appearance of the menses

These puberic changes in both sexes are brought about by an ordered interaction of internal incretions of the ductless glands which differ in the two sexes The trigger mechanism which brings about these biological changes still remains a mystery however Under normal circumstances there would seem to be an involutional stimulus of unknown origin which primarily stimulates the pituitary gland or the sex organs to open the symphony It would seem most probable that this originates in the pituitary

It was stated in discussion of the pituitary that there were two gonadotropic hormones (namely F S H and L H see page 891) The former influences the seminiferous tubules and the development of the follicles of the ovary and the latter the luteinization of the follicles and activates the interstitial cells of the testes There may also be produced two gonadotropic incretions in the sex glands which counterbalance those of the pituitary This however is still in the realm of speculation based on a modicum of suggestive evidence

It would now seem proper to discuss separately the various abnormalities of the sexual development and function of the two sexes (J C M)

Abnormalities of the Male Gonads

1 Hypergonadism
2 *Hypogonadism*
   (a) Primary hypogonadism (eunuchism)
   (b) Secondary hypogonadism (eunuchoidism)
3 Male climacteric
4 Sterility

1 **Hypergonadism** —It is doubtful whether any clear syndrome of primary overactivity of the male gonads in either phase can be clearly recognized Increase of libido which is a psychological phenomenon must not be confused *with hypergonad activity*

Precocious sexual development has been found in overactivity of the pituitary adrenal thymus and pineal glands but these cannot be considered as primary hypergonadism but rather an acceleration of the time factor in sexual evolution A distinction must be drawn between anatomical development and functional activity This is well illustrated in the life history of acromegaly

2 **Hypogonadism** —The clinical features resulting from hypogonadism will be determined to a large extent according not to the cause but to the

Destruction of both testes by inflammations such as mumps or syphilis bilateral destructive tumors or trauma (bilateral castration) is the other group of causes of primary hypogonadism and requires no further comment

(2) *Secondary Causes*—These rest outside the testes themselves and are chiefly represented by *hypopituitarism or any hormonal or combination of hormonal defects* which prevent descent of the testes

Diagnosis—It has already been mentioned that hypogonadism is quantitative To meet this variation it is customary to make a clinical distinction as to degree into eunuchism and eunuchoidism The former designates complete absence of testicular function due to complete destruction of both testes as mentioned above The latter applies to a partial reduction in function which may be due to the primary causes such as undescended testicles and to the secondary causes

The diagnosis might seem quite simple until one comes to analyze in detail *the fundamental cause because upon this rests the success of treatment*

The anatomical diversions give the lead but they cannot provide the final answer in many cases as to the qualitative and quantitative functional disturbance This may be obtained through a series of endocrine assays This depends upon the assay of urinary testosterone which would indicate a quantitative activity of the *interstitial cells of the testes* On the other hand an assay of the F S H (see page 891) would give a lead as to the activity of the gonadotropic hormone of the anterior lobe of the pituitary Another method of approach is a biopsy of the testicle But in this there is always that chance fallacy of a minute piece of tissue not being representative of the whole Finally there is the response to L H (see page 891) in the form of A P L and other trade names

Treatment—It is obvious that in cases of undescended testicles a plastic operation might be of benefit Though this is often wishful thinking it should be seriously but cautiously considered

In all other cases there is the alternative of (1) stimulation therapy with gonadotropic hormones and (2) substitution therapy with male sex hormones

It would be expected that in cases of eunuchism due to primary causes the former would be of little value as there would be nothing to stimulate However in eunuchoidism due to such causes and in cases of undescended testicles stimulation therapy may produce good results The use of A P L the gonadotropic factor in human pregnancy urine also called chorionic gonadotropin acts as a stimulus *to the interstitial cells of the testis* thus producing male sex hormone It has been demonstrated that descent of the testis may be brought about by such means It should however be used with caution in respect to where the testes are lodged If they are within the abdominal cavity such treatment is apparently contraindicated When all is said the treatment of these cases is still in a state of flux each one being treated independently or it may be said on an experimental basis

On the other hand in eunuchism where there is complete absence of testicular function the problem is more direct *Where this condition develops* after puberty one is faced with the decision as to whether the results are sufficiently inconvenient apart from impotence to warrant treatment This is a

are rare On the other hand hypogonadism due to mechanical interference with descent of the testes is relatively common It has been demonstrated that the testes develop and function better in the scrotum than when they remain in the abdominal cavity, and there is a quantitative variation depending upon their position between these two sites

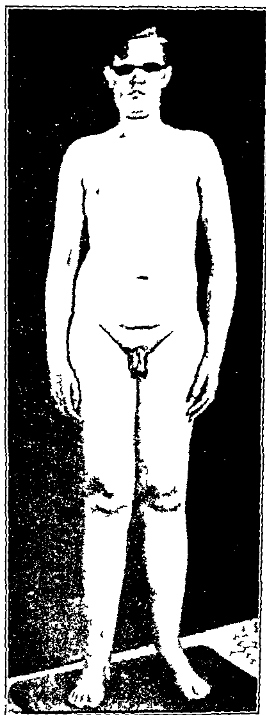


Fig 36 —Photograph of [illegible] ung man ag[illegible] twent four H[illegible]ight [illegible] 9 weight 1[illegible]1 pounds, basal metabolic rate [illegible] A case of [illegible]gonadism and eunuchoidism Note the undeveloped external genitalia the [illegible]cate limb [illegible] algum narrow shoulders broad hip and the lack of obesity

In fact the question of sterility is a most complex problem If it is to be analyzed seriously the man and wife should be referred after due explanation to a specialist in the subject as the problem requires a thorough exploration of both partners In fact in the last analysis it is not a matter which should be within the diagnostic and therapeutic purview of the physician

There is often a confusion in the interpretation of the terms *sterility* and *impotence* in the male In the former there is not necessarily a lack of priapism although there is a deficiency of efficient spermatogenesis In the latter there is usually an incapacity to copulate although by artificial methods it may be proved that spermatogenesis is normal When cases of impotence are considered the normal decrudescence of sexual desire inherent in the advancing decades should not be included Rather it should be restricted to those decades when normal sexual activity would be expected

Impotence in the true definition of the term is a psychological reaction if organic neurogenic pituitary or local penile causes can be excluded Therefore the indiscriminate use of stimulant or substitution therapy must be condemned unless it be a secondary adjuvant to psychotherapy and then only in the hands of experts

Abnormalities of Female Gonads

1 Hypergonadism
2 Hypogonadism
   (a) Primary hypogonadism (eunuchism)
   (b) Secondary hypogonadism
   (c) Virilism
3 Menstruation
4 Sterility

1 **Hypergonadism** — A clear line of distinction must be drawn between hyperfunction of the gonads as represented by an exaggerated development of the primary and secondary sex characteristics and an increase of sexual desire The latter is usually of psychic origin and may occur quite independently of the former Its causes must be sought in the realm of local acquired organic genital or systemic lesions or through psychologic exploration

(a) Primary precocious sexual development is due to ovarian tumors These are either composed of granulosa cells or are of the order of teratomata In the female when these lesions occur all the signs and symptoms of puberty may develop at an early age These in no way differ from those to be expected in adult life

(b) Secondary precocious sexual development is caused through suprarenal tumors The characteristics have been described under Pubertas Precox in the section on Diseases of the Adrenal Glands and need not be repeated here

(c) Hypergonadal function may develop as part of a general overdevelopment This is commonly found to be a part of pituitary hyperfunction as seen in acromegaly It is but part of this general condition and shares in its manifestations with other organs and systems (see page 895)

personal question which has to be decided individually That procreative powers can be revivified is a vain hope that has been put forward by some of our charlatanish colleagues

When probable eunuchism is manifest before puberty substitution therapy is indicated in the hope that this skeletal and epidermal state may be at least mitigated This is best accomplished by the use of testosterone propionate in doses of 25 mg three to seven times a week parenterally Methyl testosterone has been advocated by mouth but this is best employed as an alternate or for sustaining therapy Implantation of pellets intramuscularly as advocated for desoxycorticosterone (see page 940) and the parenteral injection of testosterone propionate in oil have also been used But after all, these methods are still in the experimental stage particularly as the maintenance dose has not yet been determined for such variable states between quantitative eunuchoidism and eunuchism

3 **Male Climacteric**—In recent years much attention has been directed by some endocrinologists and psychiatrists to what they are pleased to call the male climacteric It seems obvious that they do not mean the slow but progressive depreciation of spermatogenesis which may occur without any decrease in libido but rather a loss of libido with vague vasomotor and emotional instability which is common talk between women of a certain age of biological insecurity whether the conversation be at a tea party a cocktail assembly the dinner table or in the privacy of the connubial bed In the opinion of the author it is doubtful whether there is enough evidence even to suggest such a physiological state in the male It seems much more probable that this is purely a psychogenic state There seems to be an irresistible desire on the part of many practitioners and even so called specialists to treat these cases with stimulation androgen therapy It must be appreciated however that this state in many cases rests on a psychological or emotional basis Therefore unless it be proved that spermatogenesis has ceased the employment of this therapy is strictly contraindicated The reason for this is that if there be even a modicum of spermatogenesis let alone a normal amount this will gradually decline under this artificial stimulation (see below under sterility)

4 **Sterility**—Sterility in the male means but one thing namely the inability to propagate due to a quantitative or qualitative reduction of spermatozoa in the ejaculation This may be brought about quantitatively by some obstruction in the seminiferous tubules the prostate or even the urethra This is therefore a problem for the urologist but it must be so determined by appropriate methods of examination

On the other hand when such anatomical conditions are excluded it may be found that the sperm may be deficient in numbers or deficient in quality This is therefore a primary defect in spermatogenesis The causes for such are manifold They range from a primary (congenital or acquired) anatomical lesion in the testicle a deep emotional crisis which for some known or unknown reason has affected the spermatogenesis (see Chapter XVI) or is the result of other endocrine deficiencies particularly inherent in the pituitary and less so in the adrenal (J C M)

In fact the question of *sterility is a most complex problem. If it is to* be analyzed seriously the man and wife should be referred after due explanation to a specialist in the subject as the problem requires a thorough exploration of both partners. In fact in the last analysis it is not a matter which should be within the diagnostic and therapeutic purview of the physician.

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Impotence in the true definition of the term is a psychological reaction *if organic neurogenic pituitary or local penile causes can be excluded.* There fore the indiscriminate use of stimulant or substitution therapy must be condemned unless it be a secondary adjuvant to psychotherapy and then only in the hands of experts.

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(d) The syndrome of obesity and overdevelopment is characterized by the onset of a rather rapid growth in height and increase in weight about the age of nine or ten years It has been seen more commonly in females These patients are taller than the standard for their age They are obese, they show premature closure of the long bone epiphysis The onset of sexual maturity may be only slightly premature, but the development of the secondary sex organs

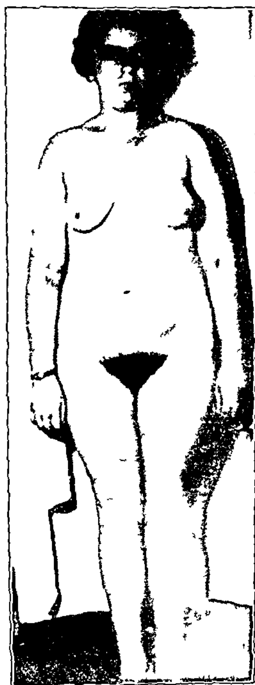


Fig 363

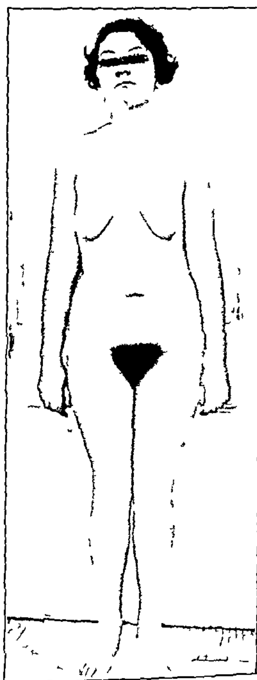


Fig 364

Fig 363 —Photograph of a girl fifteen years of age who showed general and premature sexual development beginning at the age of ten

Fig 364 —Photograph of the same patient shown in Fig 363 after treatment with thyroid extract

and characteristics after the onset is very rapid and these girls have the appearance of mature women. The mental status is usually normal but they may show a prematurity in their mental attitude. This condition should be distinguished from Frohlich's syndrome, the only common feature of the two being the obesity.

The *diagnosis* of these conditions gives little trouble as they are usually self evident to the observer. The syndrome of obesity and overdevelopment does not lead to any real abnormality and is chiefly of importance where age groups are likely to be treated alike without due allowance being made for individual variations in sexual and mental development.

The *treatment* of the primary group is removal of the ovarian tumor. The secondary group has been dealt with elsewhere.

2 Hypogonadism —

(a) *Primary hypogonadism*

Total hypofunction of the gonads in the female before puberty results in *female eunuchism*. There is the expected abnormal growth of the long bones, scanty hair growth on the mons and in the axillae, and subcutaneous fat does not accumulate to form the rounded contour of the typical female figure. The buttocks and thighs are flat, the breasts mannish, and menstruation does not occur. There is no sexual desire and the social sense is lacking. The pelvic organs remain small, and the vagina and labia remain undeveloped.

The *diagnosis* as a rule is not made until after puberty has been long delayed and the parents or the patient herself become worried about her lack of maturity. It has usually to be differentiated from other causes of amenorrhea, and a complete examination in the nude to ascertain the absence of proper physical female development is imperative. A hasty diagnosis should not be arrived at, as delayed pubescence is comparatively common. Lesions in the other ductless glands as well as organic diseases and intoxications must not be overlooked. (See below.)

The *treatment* at present is largely experimental and every case should be considered as an individual problem. All factors which may possibly in any way have a bearing on ovarian function must be thoroughly analyzed by biochemical methods and such treatment as may be indicated should be given a trial.

(b) Total hypofunction *of the gonads in the female after puberty is perhaps* best represented by the menopause. This however is often a gradual evolution that may take months or years before the complete clinical picture is produced. More striking examples are found in women who have been subject to a bilateral oophorectomy or have received intensive deep x ray therapy *with total destruction of ovarian function (see below.)*

(c) Virilism should be restricted to women in whom masculine characteristics appear after a normal feminine development has occurred. It is usually associated with cortical tumors of the suprarenal glands. The skin becomes coarse and greasy. There is hirsutism with a masculine distribution of the pubic hair and a mustache and beard are usual. The clitoris enlarges and the labia, uterus, ovaries and breasts atrophy while the voice becomes deep and harsh and there is a reversal of sex interest.

3 **Menstruation**.—The appearance of the menstrual flow has been a matter of wonder, superstition, taboo and religious and hygienic regulation since the earliest record of history. There is much evidence to indicate that it was considered by many races and religions to have a significant relation to ovulation or, from a more practical point of view, to propagation. This was entirely the result of practical experience or what might be called empiricism. But it is interesting to note the periods of social seclusion or sexual abstinence which were enjoined after the menstrual period. Indeed, our knowledge of the manner of the menstrual cycle was one of comparative ignorance up to the past decade or so. The means, both surgical and medical, employed to correct any of its abnormalities of timing or degree is ample evidence of this. In fact it may take another decade or so before some of these methods are discarded and replaced by a more rational therapy based upon known endocrinological concepts. It is not to be inferred from this that all is known about menstruation, but evidence is accumulating rapidly to clarify the problem.

In common with all biological cycles, it is well to start at some point in order that the sequence of events may be followed with eventual return to the starting point. But before this is undertaken, it must be appreciated that the full psychosexual development is under the stimulus of the anterior lobe of the pituitary gland. This not only initiates but continues to control or perpetuate the sexual activity during the procreative life of the female.

The time comes when, through this stimulus, an ovum matures and breaks away from the ovary into the vast void of the peritoneal cavity, but withal it is directed to the fimbriated funnel of the Fallopian tube (right or left or both). Coincident with the normal development of the ovum and its release there is, from the follicular cells of its origin, secreted estrogen. The purpose of this incretion is to cause growth of the endometrial mucosa and exuberance of the vaginal epithelium to facilitate coitus. But as the follicle closes, the type of cells changes from a follicular to a thecal character, which forms the corpus luteum. Not only does their form change but also their function. The corpus luteum soon begins to secrete progesterone which, as its name would imply, still further acts to prepare the uterine mucosa by further growth to receive the fertilized ovum. If, however, this does not occur, this exuberant uterine mucosa breaks down and is extruded in the form of menses, which consist of nonclotting blood and fragmented mucosal debris. On completion there is left the basal layer of endometrium which during successive days rebuilds the mucosa in preparation for the succeeding cycle.

There are now several points which must be considered.

1 Ovulation is, as a rule, symptomless; in other words, it is a seemingly unconscious process. In certain cases, however, it is accompanied by painful sensations called "mittelschmerz."

2 It is important when investigating the cause of sterility between two partners to determine whether ovulation really does occur. A fair index of this may be revealed by a rise of body temperature at the time of ovulation. This is ascertained by recording the rectal or vaginal temperature each morning after sleep but before rising. An elevation of the body temperature to 99° to 100° F, or more at this time, as compared to the so-called normal, is

strongly significant of ovulation It must however be controlled with the temperature in the intermenstrual cycle so that other causes may be eliminated

Ovulation having occurred there is initiated a series of events which are almost perfect in their sequence When the ovum has been released the site closes and the cells remaining change from follicular to thecal which form the corpus luteum These cells take on a new although temporary function to secrete progesterone which accelerates and accentuates the growth of the endometrial mucosa to await the arrival of the impregnated ovum if and when this occurs So the house is ready for habitation If however nidation is not accomplished the prepared endothelium breaks down and is discharged in the form of menses There now occurs a period of relative biological quiescence until the next ovum matures and is discharged This is commonly called the safe period when impregnation is reduced to a minimal hazard But this is dependent upon a regular cycle of events which like all such have their exceptions

Disturbances of Menstruation —

Amenorrhea —Menstruation may never be established If this be associated with dwarfism the cause must be sought elsewhere particularly in the pituitary gland *It has been referred to above It is rather a symptom than a* disease and as such a detailed repetition of its characteristics might only lead to confusion Particular attention should be directed to pituitary dwarfism (see page 906) Frohlich s syndrome (page 897) and Simmonds disease (page 899)

Retarded growth and sexual development may in addition occur from a variety of organic infections and other causes such as cretinism infantile myxedema congenital heart disease birth palsy celiac disease rachitis lead poisoning congenital syphilis tuberculosis hookworm infestation pellagra etc There have been attempts to classify the symptoms and signs of the various clinical syndromes into different groups depending upon whether the principal manifestations are morphologic or mental and to insert an intermediate or unknown group where the causes and manifestations are supposed to rest upon some unknown biochemical factor or to be associated with a perversion of intermediate metabolism

When growth of stature is normal the pituitary gland may be exonerated *It seems most probable that the syndrome is primarily ovarian in origin* They continue to have the childish configuration of skeletal and genital development (without the secondary sexual characteristics) There is no constant nutritional pattern in other words they may be obese normal or thin

The most common cause of amenorrhea is pregnancy which in time reveals itself But during the procreative period of women emotional and nutritional factors may play a prominent role A striking example of this was observed *among female internees during the last war It has been difficult to* determine which was the dominating factor but it is well known that either independently may produce this result and combined even more so The amenorrhea of anorexia nervosa is probably a summation of these factors in sequence as it frequently follows an emotional insult and precedes the in

occur These examples point to the sensitive response of ovarian function in common with other physiological functions which may be grouped within the orbit of "psychosomatic" medicine (see Chapter XVI)

Menopause—Finally, there is the amenorrhea of the menopause It must be appreciated that this is not necessarily an explosive or sudden biological event In many instances the regularity and degree of menstrual flow may decline in proportion to estrogen production There is however a minimal level of this below which menstruation ceases, but this does not rule out the possibility of an occasional upsurge of estrogen which may cause a moderate even to an excessive menstrual flow at irregular but diminishing frequency The normal menopause usually begins in the midforties Instances have been reported as early as the twenties and as late as the seventh decade The rapidity of its completion varies from an almost explosive suddenness to a prolongation extending into years

The symptoms and signs of the normal menopause and that artificially produced by castration or radiation vary only in time and duration of the evolution They may be grouped under the following

Menstruation Irregularity of the menstrual periods as regards the interval, duration and quantity is usually an early sign with eventually complete cessation Slight recurrences and continuous "spotting" should always suggest uterine cancer until proved to the contrary but this may occur during the course (and particularly after the withdrawal) of therapy with estrogenic substances

Vasomotor instability is represented by hot flushes tachycardia, palpitation, sweating vertigo tinnitus and syncope Epistaxis has been considered common but is mostly associated with hypertension The occurrence of this disturbance of circulatory function has been considered elsewhere (see page 373)

Emotional instability is quite characteristic of this period Women are then subject to irritability to worrying over trifles are exacting and suspicions are easily aroused These may take the form of various phobias which may even assume the proportions of hallucinations and delusions Acute depression sometimes occurs Sexual desire usually wanes but in some women it is maintained and may even become conspicuously increased

Anatomical changes are principally confined to an atrophy of the sex organs The ovaries become fibrotic the uterus is reduced in size and is firmer the vaginal glands atrophy with decreased secretion the labia shrink and the breasts become shrivelled and flabby An increase of weight is common

The *diagnosis* is not difficult if a careful history and examination are carried out It is most likely to be confused with neuroses or cardiovascular disturbances All other organic endocrine and psychic possibilities should be excluded Its very obviousness may permit sins of omission as it is in the fifth decade that many diseases of later life have their beginning such as diabetes mellitus, pernicious anemia hypertension, myxedema and cancer

The *treatment* of either spontaneous or artificial menopause sometimes offers considerable difficulties In a general way all disturbing mental and physical factors should be eliminated The specific treatment should be conducted along the following lines Estrogenic substances may be administered either

by injection or by mouth Hot flushes serve as a good criterion for following the effect of the therapy It is probably best to begin with large doses (10 000 I U) of the estrogenic substance intramuscularly three times a week until relief is obtained, then it may be decreased until a minimal effective level is found Some estrogenic substances are said to have a more prolonged action than others Oral therapy with natural estrogens may be effective in milder cases or as an adjuvant to the injections The synthetic estrogen (stilbestrol) has been widely used in certain countries recently Its advantage is its marked activity while its disadvantage is nausea and gastrointestinal disturbances in a certain proportion of cases and more severe disturbances in a few

As time passes improved synthetic preparations of compounds with estrogenic properties have been prepared which have no toxic effects They are prepared in amounts of 1 25 mg per tablet under the trade names of Premarin and Konestrin The usual dosage is 2 to 4 tablets a day but the response varies considerably from patient to patient and therefore each case must be assessed individually on the basis of trial and error in order to accomplish the best results

It must be appreciated that there may be considerable emotional trauma inflicted by the thought that the young woman is biologically imperfect Therefore it is often necessary to attempt to remove this inferiority by substitution therapy A course of estrogen for a period of three to four days is given then a course of progesterone is added for ten to twelve days This may bring about an artificial menstrual flow Then for a period of fourteen days after it begins the therapy is withdrawn This therapeutic cycle should be repeated for six to twelve months On its cessation occasionally fairly normal menstrual cycles may continue even in what might have appeared to be cases of obstinate hypofunction The cause of this is unknown It has been suggested that it is a reverse effect upon the pituitary gland If spontaneous menstruation does not occur after such treatment it is then optional on the part of the patient as to whether this substitution therapy should be continued It is sometimes indicated to advise strongly that it should be continued so as to relieve to some degree or entirely the emotional trauma

Menorrhagia —This term is used to designate an excessive menstrual flow It would therefore most likely be due to an overactivity of estrogen and/or progesterone leading to abnormal endometrial hyperplasia The occurrence of this may be related to three divisions of time from the menarche to the menopause These are in chronological order (1) a number of years after menstruation has begun from the 14th to 25th year (2) from the 25th to 35th year and (3) from the 35th to 45th year before the menopause is complete These are rough demarcations and must be so considered Furthermore menorrhagia does not occur in all women by any means

Menorrhagia in the first and third divisions would seem to rest in most instances on a similar basis The first menstrual period does not indicate that the regular ovulation cycles have been established In succeeding cycles the ovarian follicles may irregularly proceed to maturation but not to ovulation Therefore estrogen may be produced but no progesterone The endometrium will in consequence continue to pile up There may be a series of nonovu

latory cycles and depending upon the number of these, so will the volume of menstrual flow when it does occur, follow an ovulatory cycle which leads to the production of progesterone. It is to be expected that if two or more nonovulatory cycles have occurred in succession the menstrual loss will be greater than if there has been only one. In the first circumstance the menstrual flow may be almost exsanguinating leading to a reduction of the hemoglobin to 40 per cent or less. After a longer or shorter period the ovulatory cycle becomes established and these occasions of excessive flow cease. This may occur irregularly with several menstrual flows normal in time and amount, and this may be followed by amenorrhea which is again followed by an excessive flow. Such may occur rarely during the greater part of the sexual life of a woman.

The final diagnosis of this condition as far as hormonal therapy is concerned must rest upon an endometrial biopsy or a study of the menstrual cells and/or the vaginal epithelium after the technic of Papanicolaou. These, however, are matters of special technic and the reader is referred to texts on gynecological pathology.

The treatment, however, is indicated in the general principles outlined above. As this is an excessively prolonged action of estrogen without progesterone to complete a normal menstrual cycle, this may be accomplished by giving progesterone for 10 to 14 days before the date when menstruation would normally be expected. By this substitution therapy the normal endometrial cycle may be completed. It often happens that after this has been continued for some months (6 to 8) the cessation of progesterone therapy is followed by menstrual periods normal in time and amount.

Androgens should never be given.

Curettage of the uterus is of very doubtful value and should be reserved for diagnosis or for use in the occasional case when it would seem desirable to be sure that all abnormal hyperplastic endometrium has been removed.

The question of hysterectomy may sometimes be faced. All measures to avoid it should be carried out. It is true that the operative risk is slight, but the psychological and emotional consequences are frequently of a serious character when a young woman in her upper teens or early twenties is faced with a prospect of biological inferiority.

It is obvious that the general condition of these patients should be maintained by supportive treatment as to diet, exercise and rest, with regular and continuous courses of iron. It is further obvious that a thorough exploration should be made of the general physical condition, especially in regard to any abnormality of the thyroid or pituitary glands.

The third division of time mentioned above is really this same process in reverse. As women approach the time of menopause it is to be expected that maturation of ovarian follicles may occur without ovulation but with a continued formation of estrogen but not of progesterone. So the menstrual cycles become irregular and excessive menstruation may occur. This, however, does not necessarily happen following all irregularities, as even maturation of the follicles may not occur until there is complete ovarian inactivity (see Menopause, page 956).

The *treatment* of menorrhagia at this time may follow the same lines as in the first period but with a difference Biological usefulness of the uterus is now reaching its termination and therefore hysterectomy does not have the same implications as it had twenty years before Further the age period for the increasing incidence of cancer is at hand Therefore a hysterectomy may serve two purposes namely the correction of the present condition and be after the manner of prophylactic surgery There are however occasional cases in which for some reason the risk of such an operation should be avoided or postponed then the substitution therapy mentioned above may be of value But in such the certainty of the diagnosis must be confirmed by histological means

The second time division is an arbitrary one and is not necessarily confined to these years but is in relation to previous pregnancies Therefore the menorrhagia may occur irrespective of the quality of ovulation In most cases it has a strictly anatomical basis in that the endometrium is shed in patches over a period of many days and not in a fairly uniform fashion as occurs normally The reason for this is not known nor can it be taken for granted that this is the case without verification by biopsy when a progesterone endometrium should be found Furthermore other anatomical lesions should be sought by a careful gynecologic examination However the functional or estrogenic menorrhagia described above should not necessarily be excluded and should be suspected when there are periods of amenorrhea followed by excessive bleeding

The treatment of these cases will depend upon the cause and should be decided upon after consultation with the gynecologist and endocrinologist

Irregular uterine bleeding should always be suspected as being due to an anatomical lesion such as uterine fibrosis cancer etc It is therefore imperative that it be given prompt attention This is particularly the case in all women over forty but at no age should it be neglected All diagnostic methods should be employed by experts

4 **Sterility** —Sterility in the female has already been dealt with to some extent under hypogonadism and absence of ovulation If however there is good reason to believe that ovulation does occur then it is a question of determining why the ovum has not reached the sperm in the first place or does not remain implanted in the prepared endometrium in the second These problems are beyond the scope of the present text and are within the role of specialists in this subject in collaboration at times with the gynecologist This is also intimately related to *habitual abortion* when it may be suspected that either the ova are frequently imperfect or the incretion of the corpus luteum is deficient If local uterine anatomical abnormalities can be excluded this would appear then to be within the realm of the endocrinologist (J C M)

Developmental Abnormalities

Abnormalities of the genital organs are found in both sexes They consist of the following hermaphroditism and pseudohermaphroditism and cryptorchidism In the female imperforate vagina bicornate uterus etc are reported These conditions are dealt with in detail in textbooks on urology and

gynecology The anatomical findings are often confusing and the detection of the exact functional disability may rest upon a careful biochemical analysis and partition J C M

DISEASES OF THE PARATHYROID GLANDS

Introduction

The parathyroid glands are four in number and normally rest behind the lateral lobes of the thyroid Their location is not always consistent in that they may be found behind the trachea or in the anterior mediastinum Their blood supply is derived from the inferior thyroid artery So far as is known, these small glands each the size of a bean, secrete a hormone which controls the calcium balance between the blood and tissues They function independently of other ductless glands although recent evidence would suggest the influence of a pituitary factor MacCallum and Voegtlin showed that the state of tetany which followed their removal could be symptomatically controlled by injections of calcium Collip, in 1925, isolated the active principle of its incretion which is called *parathormone*

With any state of hypoparathyroidism spontaneous or postoperative the blood plasma calcium drops from its normal level of 10 mg per cent with an associated rise in the plasma phosphorus If the blood calcium falls below 7 mg per cent a syndrome known as tetany appears Dogs which have had their parathyroid glands removed frequently develop bilateral cataract The author has seen one such case in a man whose parathyroids were accidentally removed during subtotal thyroidectomy

A disease of the bones is now recognized to be due to hyperparathyroidism This is known as osteitis fibrosa cystica and is caused by the irregular withdrawal of calcium from the bones with the development of cystic areas The etiological lesion is either a tumor or hyperplasia of one or more of the parathyroid glands

Calcium Metabolism

The normal plasma calcium is 10 mg per cent of which about 60 per cent is ionized and the remainder is bound to protein The control of the percentage of the total calcium that is ionized is not understood The ionized fraction is the functionating fraction in the matter of neuromuscular irritability and the deposition and withdrawal of calcium from the bones and the teeth No method is available which is exact and practical for the determination of this ionized fraction thus calcium determinations upon blood denote total calcium only

The body calcium is derived from the food The daily requirement is about 1 0 gram Milk is the main source of supply and without 50 per cent of the requirement being taken in that form a deficiency is usual Calcium absorption is variable and excretion takes place by the urine and the feces The child excretes a greater percentage of the total by the feces than the adult The blood calcium is remarkably constant The balance of ionized calcium between blood plasma and tissues (bone and teeth principally) is controlled by the parathyroid hormone A deficiency of this hormone results in

a fall of the plasma calcium with an increased bone storage and a lessened excretion in the urine An excess of parathyroid hormone causes an elevation of blood calcium, a withdrawal from the bones and teeth and an increased excretion in the urine A very low blood calcium (6 mg per cent) may be seen in chronic nephritis associated with low serum proteins These patients do not have tetany because the plasma calcium deficiency occurs at the expense of the nonionized fraction which is bound to protein

Hypoparathyroid Function

Tetany and cataracts are the two pathological states known to follow deficient parathyroid function Tetany is a clinical syndrome which may have several causes

Tetany (Spasmophilia)

Definition —Tetany is a state of increased irritability of the neuromuscular control In its mildest forms it can be detected by the electrical reactions of muscles, and by abnormal responses characteristic of this state In its more active form spasms or cramps of muscle groups and tetanic convulsions occur

Etiology —The causes of tetany fall into two main groups (1) where there is a lowering of the physiologically active serum calcium, and (2) where an alkalosis with an increase of the pH of the blood plasma develops The ionized serum calcium is lowered by (1) removal of the parathyroids (2) administration of alkaline phosphates (Na HPO_4), and (3) in certain types of rickets and osteomalacia An alkalosis with an increase of the pH of the blood plasma may occur from (1) hyperpnea (2) persistent vomiting and (3) the administration of excessive alkali (see Alkalosis page 866)

Parathyroid tetany follows removal of the parathyroid glands which may occur accidentally at the time of thyroidectomy The blood calcium falls and there is a concomitant rise in the inorganic phosphorus Excessive intake of alkaline phosphates (Na HPO_4) will likewise lower the blood calcium and raise the phosphorus Infantile tetany occurs in children with rickets and hypocalcemia Osteomalacia or adult rickets (see page 803) also may show hypocalcemia leading to tetany In all of these low blood calcium types of tetany it is the ionized fraction of the serum calcium that is reduced When the total blood calcium reaches a level of 7 mg per cent (normal 10 mg per cent) tetany may appear In diseased states where there is a great lowering of the serum proteins the total blood calcium may fall even to 6 mg per cent without tetany because the loss occurs at the expense of the fraction bound by the serum proteins which is not physiologically active

Hyperpnea may be voluntary follow hot baths or occur in hysterical patients It results in a primary CO deficit of the blood or a noncompensated gaseous alkalosis and may progress to an abnormal increase of the pH of the blood Persistent vomiting causes an excessive loss of hydrochloric acid and consequently a reduction of the blood chlorides the latter being compensated for by an increase of the plasma bicarbonate and an alkalosis (gastric tetany) This is commonly seen in pyloric obstruction Administration of an excessive amount of sodium bicarbonate also may cause an increase of the plasma pH

The CO_2 capacity of the blood may rise to over 100 volumes per cent Tetany occurs with alkalosis (relative or absolute) when the pH of the blood reaches 7 6 In the low calcium tetanies there is no evidence of an alkalosis

Symptoms and Signs —Mild or latent tetany may have few symptoms, but certain signs can be elicited Of these, Erb's sign is the most constant The motor nerve in tetany will respond to an electrical stimulus with a far weaker current than is required to produce a minimal reaction in a normal person Normally the cathodal opening response requires more than 6 milliamperes while in tetany a response is obtained with less than 5 milliamperes Also tetanic contraction can be obtained with a weaker current on anodal opening than with anodal closure This is the reverse of the normal response Chvostek's and Trousseau's signs are also indicative of tetany The former is a spasm of innervated muscles by tapping the facial nerve just anterior to the ear at the point where it emerges from the stylomastoid foramen The latter is a typical tetanic spasm of the muscles of the forearm and hand elicited by compression of a nerve trunk on occlusion of the arterial blood supply in the upper arm The hand assumes a rigid flexed posture with the fingers flexed at their metacarpophalangeal joints and the thumb adducted (Fig 365)

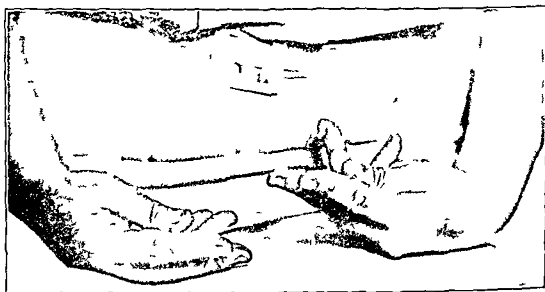


Fig 36 —Parathyroid tetany showing Trousseau's sign

When tetany is active these muscular spasms occur spontaneously All voluntary muscles may undergo clonic or tonic contractions and muscle cramps and stiffness are common With involvement of the glottis breathing is difficult and noisy (laryngismus stridulus) Glottic involvement occurs mainly in children, and is accompanied by severe cyanosis and complete cessation of respiration may follow The diaphragm may also be affected producing severe epigastric pain and with spasm of the intercostal muscles seriously interfere with respiration In fact no muscle may be exempt including the esophagus, bladder vagina and intestines Tetany in its severest form may cause generalized convulsions and death

TABLE XII

ANALYTICAL FINDINGS IN VARIOUS TETANIES AND RELATED DISORDERS

(From Cecil: Text Book of Medicine, 3rd edition, W. B. Saunders Company, Philadelphia, 1[illegible]3, page 1[illegible]4[illegible])

DISEASE	BLOOD PLASMA VALUES				EXCRETION DURING LOW CALCIUM DIET			
	CALCIUM	PHOSPHORUS	PH	PHOSPHATASE	URINE CA.	URINE P	FECES CA	FECES P
Tetany due to parathyroid deficiency	low	high	normal		low	low	normal	normal
Hyperparathyroidism	high	low	normal	high	high	high	normal	normal
Steatorrhea—difficulty in absorbing calcium from the intestines	normal or low	low	normal	normal or slightly high	low	high	high	normal
[illegible]tional er[illegible] from deficiencies and rachitis	normal or low	low	normal	high	low	low	low	low
Hyperthyroidism	*normal*	*normal*	*normal*	high	very high	very high	high	high
Paget's disease (Osteitis *deformans*)	normal	normal	normal	very high	*No marked variation*			
Gastric tetany	normal	normal	increased					
Hyperventilation	normal	normal	increased					
Excessive bicarbonate ingestion	normal	normal	increased					

Diagnosis.—Tetany offers difficulty in diagnosis only in a latent form. Chvostek's and Trousseau's signs may be absent, but Erb's sign will always be present. The blood will show the lowering of the serum calcium or a state of alkalosis. It is differentiated from tetanus, strychnine poisoning, and hysteria. It must always be remembered that tetany is a sign of a systemic disturbance and not a disease in itself.

Prognosis.—The prognosis largely depends upon the causal factor of the tetany. When this is correctly recognized, it can be relieved by parathyroid extract, calcium salts or acid administration. It is usually possible to detect and remove the basic cause if it be carefully sought and thus a cure may be established.

Treatment.—In the treatment of tetany, recognition of the disturbed physiology is essential. *All forms of tetany improve temporarily with acid therapy* on account of the acidosis reducing the irritability of the neuromuscular control. Ammonium or calcium chloride, 6 to 8 grams a day, will be effective. These acid producing salts have a rapid effect upon the symptoms and increase calcium absorption. By reduction of the alkalinity of the blood relief can be obtained with no change in the plasma calcium. Calcium chloride is especially effective in that it supplies calcium in addition to reducing the blood alkalinity. *To cause more lasting results treatment must be specific.*

The following procedures are recommended:

1. **Tetany Due to Low Blood Calcium.**—

A. Parathyroid Tetany.—For rapid relief of symptoms, ammonium or calcium chloride by mouth or calcium gluconate intravenously is usually promptly efficacious. Calcium lactate in large doses, 4 to 12 grams a day,

The CO_2 capacity of the blood may rise to over 100 volumes per cent Tetany occurs with alkalosis (relative or absolute) when the pH of the blood reaches 7 6 In the low calcium tetanies there is no evidence of an alkalosis

Symptoms and Signs —Mild or latent tetany may have few symptoms, but certain signs can be elicited Of these Erb's sign is the most constant The motor nerve in tetany will respond to an electrical stimulus with a far weaker current than is required to produce a minimal reaction in a normal person Normally the cathodal opening response requires more than 6 milliamperes while in tetany a response is obtained with less than 5 milliamperes Also tetanic contraction can be obtained with a weaker current on anodal opening than with anodal closure This is the reverse of the normal response Chvostek's and Trousseau's signs are also indicative of tetany The former is a spasm of innervated muscles by tapping the facial nerve just anterior to the ear at the point where it emerges from the stylomastoid foramen The latter is a typical tetanic spasm of the muscles of the forearm and hand, elicited by compression of a nerve trunk on occlusion of the arterial blood supply in the upper arm The hand assumes a rigid flexed posture with the fingers flexed at their metacarpophalangeal joints and the thumb adducted (Fig 36)

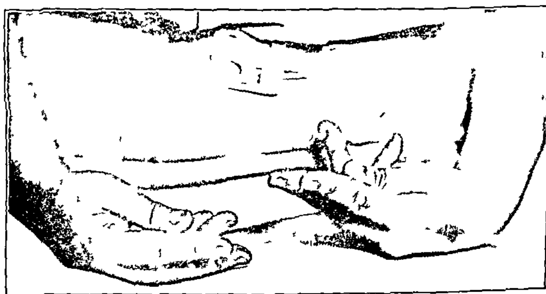


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glands There may be an adenomatous growth of one or more glands or a *general state of hyperplasia Rarely has it been possible to palpate the hyper plastic glands or a tumor*

Symptoms and Signs—The onset is usually insidious with general lassitude weakness and pains in the bones Later there is loss of appetite with a low blood pressure Physical examination may disclose tender areas on the long bones The laboratory findings are of special importance The blood *calcium is raised (normal 10 mg per cent) to a level of even 15 mg per cent* in severe cases There are an associated lowering of the blood phosphorus and an increased excretion of calcium in the urine This mobilization of calcium



Fig 366—X ray of b n s in a ca f o teitis fibrosa cyst ca due hyper parathyroid function

from the bones results in thinning of the skeleton and patchy absorption of the bone trabeculi with the development of the characteristic bone cysts which can be seen by x ray The bone absorption results in an increased activity on the part of the bone osteoclasts with the formation of giant celled bone tumors The increased plasma calcium concentration often leads to the for*mation of both renal and biliary calcium calculi* The hypercalcemia in time results in premature arteriosclerosis and chronic nephritis with nonprotein nitrogen retention

Diagnosis—The diagnosis may be suggested by the history and the physical examination but it ultimately depends upon the laboratory findings In the meantime the condition may be called myalgia lumbago, neuritis, arthritis,

is of value in chronic cases Parathyroid extract (parathormone) 50 units a day, will raise the serum calcium at the expense of the calcium stored in bones and other depots The physiological effect starts in four hours, when given intramuscularly and lasts for twenty four hours If continued for a protracted period of time it is capable of producing hypercalcemia Continued dosage must be checked regularly by determining the blood calcium With protracted administration a tolerance is acquired which necessitates the use of increasing dosage Recently dihydrotachysterol (A T 10) has been used in parathyroid tetany with excellent results It is given by mouth in doses of 2 c c daily, but hypercalcemia must be looked for

B *Alkaline Phosphate Tetany* —This type is largely experimental, and immediate relief of symptoms can be obtained by discontinuance of the basic phosphate and the administration of acids

C *Infantile Tetany (with Rickets)* —Any procedure that will produce an acidosis will relieve the symptoms Ammonium and calcium chloride acid ammonium phosphate, hydrochloric acid, and a ketogenic diet have been used Methods that raise the blood calcium, parathyroid extract or calcium gluconate are temporarily effective Institution of prompt treatment to cure the rickets is essential For this vitamin D in irradiated ergosterol or a cod liver oil concentrate may be used Ultraviolet light and sunlight are most helpful

D *Tetany in Osteomalacia* —Treatment should be the same as for tetany with rickets

2 **Alkalosis with Tetany** —

A *Hyperpnea Tetany (Uncompensated Gaseous Alkalosis)* —Treatment depends upon alleviating or removing the neurotic causes of the overventilation, and rebreathing a 5 per cent CO_2 and oxygen mixture Acidifying measures will reduce the blood alkalinity but do not strike at the fundamental cause (see Chapter XVI)

B *Gastric Tetany (Loss of Chlorides)* —Ammonium chloride or hydrochloric acid in therapeutic doses will give prompt relief Intravenous hypertonic (5 per cent) NaCl solutions are helpful Cure will depend upon relief of the basic cause pyloric stenosis intestinal obstruction paralytic ileus etc

C *Tetany from excessive sodium bicarbonate therapy* is promptly relieved by the cessation of this and the intravenous injection of hydrochloric acid in 0 5 per cent solution

Parathyroid Cataract

The incidence of bilateral cataracts in the dog after removal of the parathyroid glands is high In man it is a rare complication of parathyroid deficiency and once established it cannot be influenced by medical means Extraction of the cataracts after they have developed sufficient maturity will restore vision The parathyroid deficiency should receive appropriate treatment

Hyperparathyroidism (Osteitis Fibrosa Cystica)

A bone disease termed osteitis fibrosa cystica first described by von Recklinghausen, is now known to be due to an excessive function of the parathyroid

toms and signs are referable to pressure effects from the tumor itself The condition of macrogenitosomia precox in children is related to a pineal tumor It is not known whether this sexual precocity is the result of increased or decreased functional activity of the tumor cells

The pineal tumors in their early stages of development frequently compress the aqueduct of Sylvius with increase of pressure in the lateral ventricles producing internal hydrocephalus Ringing in the ears headache *nausea projectile vomiting and papilloedema follow* undoubtedly due to increased intracranial pressure Further symptoms and findings depend upon the area of the brain involved, and the cranial nerves compressed The presence in a child of the findings characteristic of a brain tumor as well as sexual precocity would justify the conclusion of the presence of a pineal tumor

Due to their location surgical removal is difficult but may be successful in the encapsulated cases Unfortunately the majority are infiltrative x ray therapy may be tried as a palliative measure

DISEASES OF THE THYMUS GLAND

The thymus gland is of epithelial origin and derived embryologically from the third and fourth branchial clefts It is located in the anterior mediastinum and weighs at birth about 12 grams It increases in size up to puberty (weight 37 grams) and subsequently undergoes a gradual atrophy

The exact function of the thymus gland is unknown No growth disturbances have ever been proved to be connected with a primary lesion

Experimentally in fowls Soli observed that thymectomy caused eggs to be laid without calcium in the shells Thymus feeding to such thymectomized hens restored a normal shell formation This work was confirmed by Riddle Rowntree has reported remarkable observations upon the results of injection of successive generations of rats with a thymus extract After the third generation the young are born in a state of precocity and their early growth and development are greatly accelerated Sexual maturity occurs early and fertility is increased When adult growth is reached the animals do not differ from the normal

Pathological Anatomy—Hypertrophy and hyperplasia of the thymus have been found After puberty the thymus undergoes regression therefore a relatively hypertrophied gland in adult life may be an arrest only of this normal cycle Tumors are the best understood primary thymus lesion They may be benign but carcinoma sarcoma and thymoma are relatively common Lymphosarcoma is the most frequent arising from the adult cell of the thymus which is of the order of a lymphocyte

Thymus Tumors

Benign and malignant tumors of the thymus cause symptoms of pressure in the anterior mediastinum Cyanosis of the upper extremities dilated veins over the upper chest tracheal obstruction esophageal obstruction and cardiac arrhythmias from vagus and sympathetic irritation are the main signs Per

and a host of other simple conditions which are not diagnoses but confessions of neglect An elevated blood calcium with a lowered plasma phosphorus associated with bone cysts, and possibly renal stones, makes the diagnosis definite Certain cases have cycles of hyperparathyroidism with periods when the blood calcium is only slightly elevated A calcium balance well controlled will show the excess urinary excretion

Complications and Prognosis —The natural history of the disease is to gradually withdraw so much calcium from the skeleton that the bones become thinned and spontaneous fractures follow Even collapse of a vertebra with pressure on the nerve roots may occur Renal and biliary calcium stones are usual and lead to infection, which is particularly important as renal insufficiency may follow

Early diagnosis and removal of the adenoma from the parathyroid gland may completely arrest the hyperparathyroidism Symptoms disappear and the bone changes and the blood calcium and phosphorus tend to revert to the normal Accordingly the prognosis rests upon early diagnosis and the successful finding of a parathyroid lesion and its removal Otherwise the disease will progress

In addition to the above lesions there has been described by Selye a condition of edema and scleroderma due to moderate parathyroid hyperfunction It would seem to have a bearing in man upon certain indefinite dermatologic trophic and vascular disturbances which are not as yet thoroughly understood particularly in relation to certain deficiency syndromes

Treatment —Successful treatment depends entirely upon finding the parathyroid lesion and its removal More than one parathyroid may be involved If extensive parathyroid removal is necessary parathyroid tetany may follow but usually only temporarily Provided two of the parathyroid glands remain a normal function can be expected During the period of redeposition of calcium and phosphorus in the depleted bones a diet high in calcium and phosphorus should be given

DISEASES OF THE PINEAL GLAND

The pineal gland is about 6 mm long and lies just over the midbrain in the median line Its physiology is not known Rather early in life it tends to become calcified thereby casting a shadow above and behind the sella turcica Rowntree has injected pineal gland extracts into rats with some evidence of abnormal development The offspring have shown an excessive growth of hair but tend to be dwarfed

Pineal Tumors

Most of the clinical knowledge concerning the pineal gland has been assembled from a study of cases with pineal tumors These tumors may be of varied nature, infiltrating or encapsulated malignant or benign The infiltrating types are the more numerous In children pineal tumors are infrequently associated with a state of sexual precocity while in adults the symp

cussion shows a broadening of the sternal dullness and x ray confirms this by revealing an enlarged shadow in the anterior mediastinum

Treatment—Treatment is unsatisfactory X ray therapy will cause a temporary decrease in size with symptomatic improvement but the fatal outcome is only delayed

Status Thymicolymphaticus

Several decades ago great interest was aroused in the autopsy finding of an enlarged thymus in an infant that died suddenly It was supposed to result from the infant s being suffocated by the enlarged thymus although signs of suffocation were not demonstrable As a consequence the chests of large numbers of children were x rayed shortly after birth and if the thymus shadow appeared enlarged they were given x ray treatment Some shrinkage of the thymus shadow followed but the controls if any did not support any specific effect More recently the validity of this interpretation has been seriously doubted There is little evidence today that sudden deaths without symptoms are due to enlargement of the thymus gland

The position of *status thymicolymphaticus* as a clinical condition has given rise to much controversy The principal difficulty has rested upon the confusion of definitions There seems little doubt that there is a clinical syndrome with the following characteristics The infant or child is well nourished and the skin thin and smooth There is general lymphoid hyperplasia of the follicles of the tongue the tonsils lymphadenopathy splenomegaly susceptibility to catarrh of the mucous membranes The thymus may be large but this must be judged in relation to its normal evolution These children are prone to infections and a hypoglycemia has been reported

The anatomical changes confirm the clinical findings but in addition there may be found diffuse lymphoid infiltration of the tissues and the bone marrow may be hyperplastic and contain diffuse and focal lymphoid deposits

It would seem best to consider this condition as constitutional rather than as a disease entity until much more is known concerning it

Sudden deaths may occur and are so often associated with anesthetics serum injections and arsenic therapy that caution should be exercised in this condition in all unusual procedures These deaths should not be laid at the door of an enlarged thymus unless symptoms of suffocation are definitely present If the thymus shadow by x ray does appear definitely enlarged irradiation may be employed but should not be considered as specific

CAROTID BODY

(Carotid Glands and Carotid Sinus)

This combination of nervous and chemical sensitive receptors in the aorta and at the bifurcation of the carotid arteries is undoubtedly an important factor in the physiologic regulation of the body These functions have been investigated extensively by experimental physiologists but as yet their role in diseases of man is but little understood

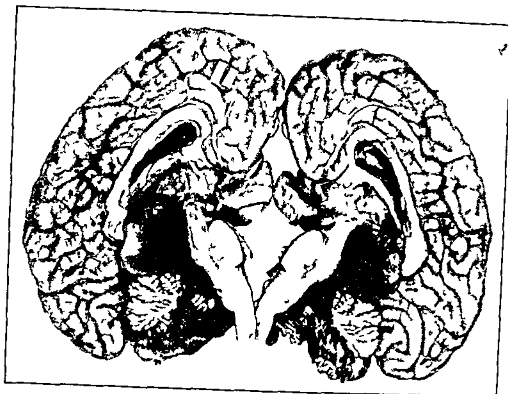


Fig 36

Fig 368

Fig 367—Photograph t n er e ct on of an ncap ul ted pineal tun o n a bo of fourteen years Complete compres ion of the aqueduct f S l ius ith hydro epl alu The syndrome of macrogenitosomia precox was not present

Fig 368—Photograph anteropo terior sect n of an n ap ulat d pineal tumor in a b y of fourteen years same case as shown in Fig 36

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The depressor or aortic nerve (a vagal branch), described by Ludwig and Cyon in 1866, and the carotid sinus innervated by a branch of the glossopharyngeal nerve, described by Hering in 1924, form undoubtedly an essential link in the regulation of the circulation and in mammals a less critical one of respiration

The carotid sinuses are localized enlargements in the wall of the carotid arteries at their bifurcation They contain nervous receptors, whereas the carotid body is a small chromophil collection which is sensitive to chemical stimuli The intimate association of these two structures is not without significance

The carotid sinus is influenced by the pressure within the carotid arteries as is the aortic nerve by that within the aorta As the pressure rises, there is an increased volley of impulses generated in the sinus, and as a result there is a reflex relaxation of the arterioles and probably also the capillaries and the large veins and a bradycardia This is general, and there is no evidence that this is in any way local As a result there is a compensatory fall in peripheral resistance in order to maintain a proper circulatory equilibrium On the other hand, there is no evidence that a low arterial pressure alone stimulates any nervous receptors to raise the peripheral resistance and thus the blood pressure The reaction to a fall in blood pressure, however, is a constriction in all types of blood vessels, a tachycardia, an increased outpouring of adrenalin and a contraction of the large veins

Denervation (or anesthetizing) of the carotid sinuses produces a permanent elevation of blood pressure which may be quite alarming There are tachycardia, extrasystoles bigeminy electrographic changes and cardiac hypertrophy

The chemical and nervous control of respiration has already been discussed (see page 324) and reference was incidentally made to the carotid body It is doubtful whether within physiological limits the carotid glands as chemical receptors influence respiration in mammals Experimentally asphyxia oxygen lack and CO_2 excess lead to respiratory stimulation Section of the sinus and carotid nerves may lead to hyperpnea in some dogs, but it is not constant nor persistent unlike the hypertension and tachycardia which are The most important finding in regard to respiration is the response of these structures to chemical stimulation by reduced oxygen tension and by the fixed acids but not by CO_2 excess and by such drugs or poisons as lobeline nicotine cyanides and sulfides

The application of these physiological observations to diseases or syndromes in man are not as yet at all clear Hyperactivity or hypersensitivity give a clear cut reaction There are acute hypotension bradycardia bradypnea and unconsciousness This result may be induced in certain persons by wearing a tight collar or neckband or even by pressure or stroking the skin over the anterior triangle of the neck It is a cause of syncope which is often overlooked

The contrary effect of paroxysmal or constant hypertension tachycardia or hyperpnea has not as yet been recognized as a clinical syndrome although there are some who claim that such is the case Atheromatous degeneration

of the carotid artery in the region of the sinus has been accused of producing such an effect This must await verification In fact this whole subject in medicine has yet to be properly explored

Christie has demonstrated an extract of a carotid gland tumor in man to contain a thermostable vasodepressor principle in high concentration Its action on the blood pressure the pulse rate and the virgin uterus was directly opposite to that of adrenalin

Tumors of the Carotid Gland

Tumors of the carotid gland are rare They may be benign or malignant Their types vary as those arising from the medulla of the adrenal glands Neuroblastomas and paragangliomas are malignant while ganglioneuromas are benign A tumor of the carotid gland has certain clinical characteristics that are helpful in diagnosis They are movable laterally but not vertically They are single nodules transmit an impulse from the adjacent arteries cause bulging of the pharyngeal wall and are of slow growth Removal has been accomplished Paragangliomas are composed of the chromaffin type of cell *and are sometimes associated with intermittent paroxysmal hypertension*

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CHAPTER XV

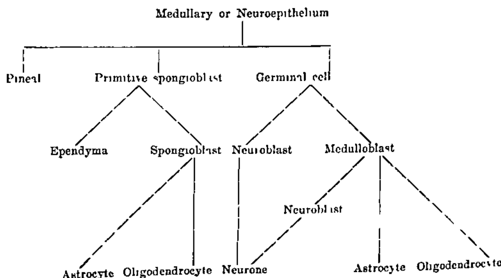
DISEASES OF THE NERVOUS SYSTEM

J N PETERSEN, B Sc , M D , C M

INTRODUCTION

The union of male and female germinal cells results in a unicellular fertilized ovum which has the potentialities of all the tissues of the adult individual The development of this fertilized ovum takes place by cell division and differentiation, and with progressive differentiation the potentialities of the dividing cell groups become progressively reduced The earliest differentiation is into the three primary layers of ectoderm, mesoderm, and endoderm, and it is from the outermost of these or the ectoderm, that the nervous system develops

The first step in this development is the formation of the neural or medullary plate, a localized thickening in the middorsal region of the long axis of the growing embryo (Fig 369) The cells of this plate undergo division which is most marked at its lateral borders, and because of this the center of the plate becomes depressed to form the neural groove As the groove increases in depth, its dorsolateral margins gradually approach one another until finally an ectodermal tube becomes separated from the remainder of the growing ectoderm and lies ventral to it This neural tube is the primitive central nervous system At the junction of neural ectoderm and general ectoderm, a further group of cells differentiates to form the neural crest from which those nerve cells which lie outside the central nervous system develop The neural tube also differentiates into three layers (Fig 370) (1) an inner ependymal layer in which are located the actively dividing germinal cells (2) a middle mantle layer made up of neuroblasts and spongioblasts and (3) an outer marginal zone consisting mostly of nerve fibers Without indicating all the intermediate steps the cellular development from the inner ependymal layer proceeds as follows (modified from Bailey)



Lining the neural tube inside and outside are the internal and external limiting membranes

The loose mesenchymal or mesodermal tissue surrounding the neural tube gives rise to the meninges, the skull and vertebral column, and also to migratory cells which invade the central nervous system and become microglia In addition it is by invasion of mesodermal elements that the blood vessels of the central nervous system are formed

In the earthworm each segment of the nervous system is almost identical to all other segments and each is a complete unit in itself As animal life in

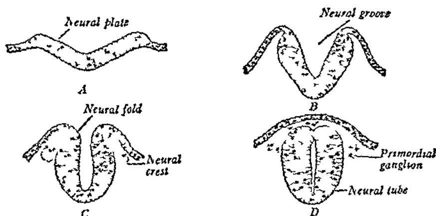


Fig 369—The development of the neural tube from the ectoderm (From Arey Developmental Anatomy W B Saunders Co Philadelphia)

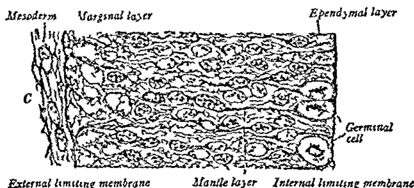


Fig 370—The cellular development of the neural tube (After Hardesty From Arey Developmental Anatomy W B Saunders Co Philadelphia)

creases in complexity and ascends in the scale of evolution, newer functions come to be located in the anterior end of the neural tube the growth of which becomes *much more rapid and is complicated by the formation of flexures* (Fig 371) It is from this increased growth and differentiation at the head end and the allocation of newer functions to this region that the brain is formed The remainder of the neural tube retains much more its original conformation and becomes the spinal cord The lumen of the tube persists as the central canal of the cord and the ventricles of the brain

The structural and functional unit of nerve tissue is the neurone which consists of the nerve cell and its processes (Fig 372) The cells vary in size

CHAPTER XV

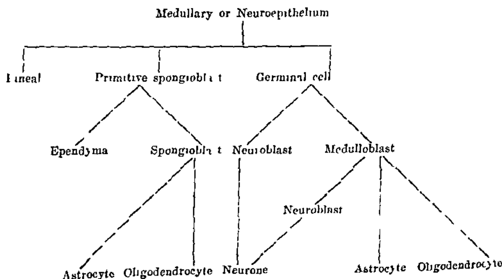
DISEASES OF THE NERVOUS SYSTEM

J N PETERSEN, B Sc, M D, C M

INTRODUCTION

The union of male and female germinal cells results in a unicellular fertilized ovum which has the potentialities of all the tissues of the adult individual The development of this fertilized ovum takes place by cell division and differentiation, and with progressive differentiation the potentialities of the dividing cell groups become progressively reduced The earliest differentiation is into the three primary layers of ectoderm, mesoderm, and endoderm, and it is from the outermost of these, or the ectoderm, that the nervous system develops

The first step in this development is the formation of the neural or medullary plate, a localized thickening in the middorsal region of the long axis of the growing embryo (Fig 369) The cells of this plate undergo division which is most marked at its lateral borders, and because of this the center of the plate becomes depressed to form the neural groove As the groove increases in depth its dorsolateral margins gradually approach one another until finally an ectodermal tube becomes separated from the remainder of the growing ectoderm and lies ventral to it This neural tube is the primitive central nervous system At the junction of neural ectoderm and general ectoderm, a further group of cells differentiates to form the neural crest from which those nerve cells which lie outside the central nervous system develop The neural tube also differentiates into three layers (Fig 370) (1) an inner ependymal layer in which are located the actively dividing germinal cells, (2) a middle mantle layer made up of neuroblasts and spongioblasts and (3) an outer marginal zone consisting mostly of nerve fibers Without indicating all the intermediate steps the cellular development from the inner ependymal layer proceeds as follows (modified from Bailey)



Lining the neural tube inside and outside are the internal and external limiting membranes

The loose mesenchymal or mesodermal tissue surrounding the neural tube gives rise to the meninges the skull and vertebral column and also to migratory cells which invade the central nervous system and become microglia In addition it is by invasion of mesodermal elements that the blood vessels of the central nervous system are formed

In the earthworm each segment of the nervous system is almost identical to all other segments and each is a complete unit in itself As animal life in

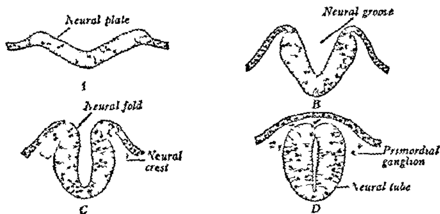


Fig 369 —The development of the neural tube from the ectoderm (From Arey Developmental Anatomy W B Saunders Co Philadelphia)

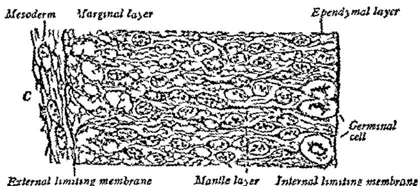


Fig 370 —The cellular development of the neural tube (After Hardesty From Arey Developmental Anatomy W B Saunders Co Philadelphia)

creases in complexity and ascends in the scale of evolution newer functions come to be located in the anterior end of the neural tube the growth of which becomes much more rapid and is complicated by the formation of flexures (Fig 371) It is from this increased growth and differentiation at the head end and the allocation of newer functions to this region that the brain is formed The remainder of the neural tube retains much more its original conformation and becomes the spinal cord The lumen of the tube persists as the central canal of the cord and the ventricles of the brain

The structural and functional unit of nerve tissue is the neurone which consists of the nerve cell and its processes (Fig 372) The cells vary in size

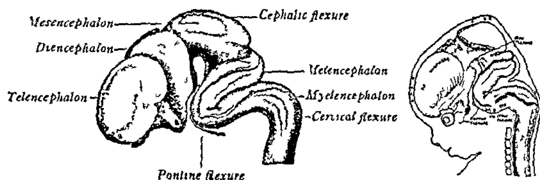


Fig 371—The development of the brain by the increased growth and differentiation and the formation of flexures at the head end of the neural tube (After His From Prentiss' Developmental Anatomy W B Saunders Co Philadelphia)

Fig 372—A nerve cell and its processes The entire structure is not in focus because of its size and the degree of magnification The neurofibrillar structure is clearly shown

and shape from the small granular cells of 4 μ to 6 μ to the large Betz pyramidal cells, in the motor or pre Rolandic cortex, which may measure 100 μ or more in their largest diameter The processes are the dendrites, through which the cell receives impulses from other cells and the axone, which may be several feet in length and which is the efferent process of the cell The individual axones are the nerve fibers which when grouped together form nerve tracts and peripheral nerves Most of the axones in the nervous system do

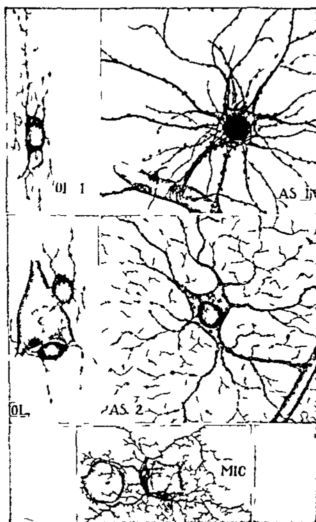


Fig 373 —The interstitial cells of the central nervous system OL and OL 1 oligodendroglia from man the former as perineuronal satellites AS 1 fibrous astrocyte with perivascular foot plate AS 2 protoplasmic astrocyte MIC microglia cell in relation to two nerve cells (From Penfield Special Cytology edited by E V Cowdry Paul B Hoeber Inc New York)

not become functionally mature until they are myelinated Myelin is a lipoid material which covers the axone as insulating material covers a wire It is formed during the latter part of intrauterine life and for several months after birth In its deposition it follows functional pathways and ordinarily sensory fibers and tracts are myelinated before motor ones

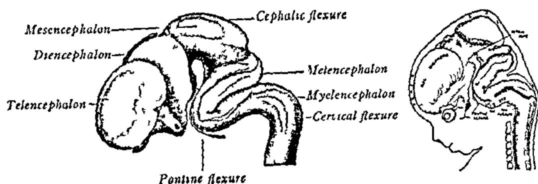


Fig. 371.—The development of the brain by the increased growth and differentiation, and the formation of flexures at the head end of the neural tube. (After His. From Arey, Developmental Anatomy, W. B. Saunders Co., Philadelphia.)

Fig. 37 .—A nerve cell and its processes. The entire structure is not in focus because of its size and the degree of magnification. The neurofibrillar structure is clearly shown.

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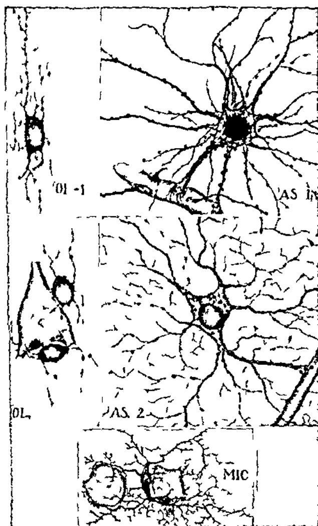


Fig. 373.—The interstitial cells of the central nervous system. OL and OL 1, oligodendroglia from gray matter, former as perineuronal satellites. AS 1, fibrous astrocyte with perivascular foot plates. AS 2, protoplasmic astrocyte. MIC, microglia in relation to two nerve cells. (From Penfield, Special Cytology, edited by E. V. Cowdry, Paul B. Hoeber, Inc., New York.)

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In fixed and stained nerve cells chromophilic Nissl granules are seen and these undergo changes, which are described later, in pathological processes In the area about the origin of the axone and in the axone itself these granules are absent, although they are present in the dendritic processes Nerve cells also contain neurofibrils, which can be shown by appropriate stains and can be followed into and through the course of the axone

The interstitial cells of the nervous system are the neuroglia and microglia cells (Fig 373) The neuroglia cells are developed from the ectoderm and consist of the astrocytes and oligodendroglia cells or oligodendrocytes The microglia cells are of mesodermal origin Astrocytes are either fibrous or protoplasmic (nonfibrous) The former occur in the white matter of the central nervous system, the latter in the grey matter These large stellate cells invariably have one of their processes attached to a mesodermal structure, either a blood vessel or the pia, and this process or expansion is known as the perivascular or pial foot The oligodendrocyte is a small cell with a darkly staining nucleus, little cytoplasm and fewer expansions than the astrocyte It appears characteristically closely applied to nerve cells, as perineuronal satellites, and also in long parallel rows in the white matter between the myelinated axones It is believed to have a secretory function concerned with the formation of myelin and it has no perivascular or pial foot such as that of the astrocyte The mesodermal microglia cells have elongated or triangular nuclei and granular expansions which are characterized by short spines at right angles to the expansion itself In pathological conditions microglia undergo profound changes and become phagocytic, a process which is described later

The nervous system is made up of grey matter and white matter The former consists of nerve cells, the latter of nerve fibers In the brain (Fig 374) the grey matter is located on the surface (cerebral cortex) and also in large nuclear masses within the brain the basal ganglia, red nucleus etc In the spinal cord (Fig 375) the grey matter is inside and the white matter on the surface Neuroglia and microglia cells are present in both grey and white matter

For purposes of description the brain is divided into (1) telencephalon or forebrain, which is divided by the longitudinal fissure into two cerebral hemispheres (2) diencephalon or between brain containing the thalamus and the hypothalamic nuclei (3) the mesencephalon or midbrain including the corpora quadrigemina red nucleus substantia nigra and various cranial nerve nuclei, (4) the metencephalon or pons and cerebellum and (5) the myelencephalon or medulla oblongata which is continuous with the spinal cord

The surface of the brain in lower mammals, such as the rabbit is smooth but as it ascends in the mammalian scale the surface becomes increasingly complex In the human being (Fig 376 and Fig 377) it is formed into convolutions or gyri separated by fissures and sulci In this way a greater surface, and so a greater number of nerve cells can exist in any given area Each of the convolutions separated by the sulci has its own name and in addition the fissures divide the brain up into larger subdivisions known as lobes

The Rolandic or central fissure separates the frontal lobe from the parietal lobe the Sylvian fissure separates the temporal lobe below from the parietal and frontal lobes above and the parietooccipital fissure which is less well defined than the others separates the occipital lobe behind from the parietal and temporal lobes in front In addition to these gross subdivisions, the cerebral cortex has been divided into a number of distinctive areas based upon



Fig 314—Sagittal section of the brain to show the grey matter on the surface and in the nuclear masses in the interior, white matter elsewhere

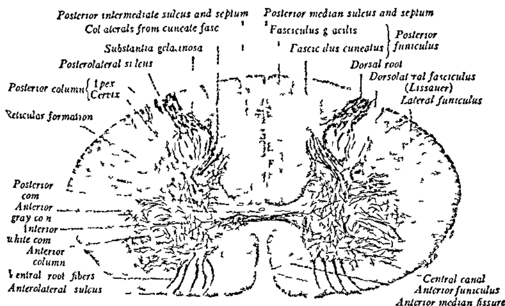


Fig 315—Drawing of a section through the thoracic segment of the spinal cord of a child stained by Pal-Weigert's method This method stains the myelin sheaths alone Tracts of white matter which have been stained are arranged around the grey matter The grey matter contains but few fibers and its nerve cells are not shown because of the selective staining (From Ranson The Anatomy of the Nervous System W B Saunders Company Philadelphia 1931)

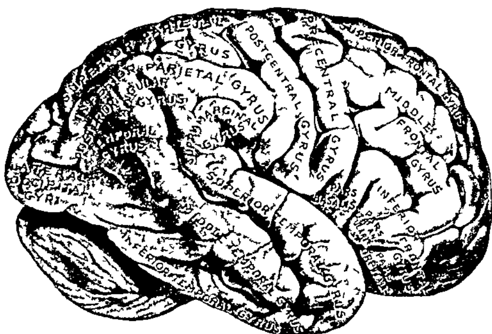


Fig 376.—Brain viewed from the right (From Tilney and Riley The Form and Functions of the Central Nervous System Paul B Hoeber New York 1923)

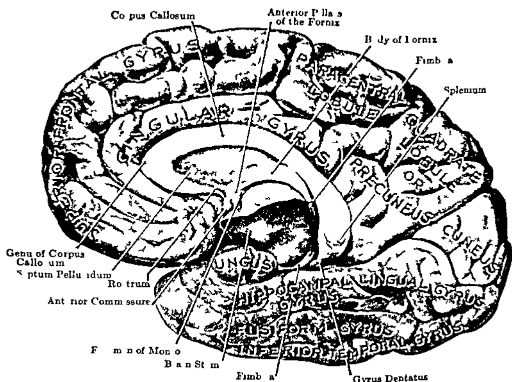


Fig 377.—Right cerebral hemisphere viewed from the left (From Tilney and Riley The Form and Functions of the Central Nervous System Paul B Hoeber New York 1923)

the architectural arrangement of the cells which form it Brodmann has differentiated 52 areas which differ in the distribution and type of cells occurring in the six layers which form the cortex

The entire central nervous system is enveloped in three coverings which form the meninges The outermost of these is the thick tough fibrous covering known as the dura mater or pachymeninges Reflections of this penetrate the longitudinal fissure as the falx cerebri and also between the inferior surface of the cerebrum and the superior surface of the cerebellum as the tentorium The tentorium divides the intracranial cavity into two parts, the

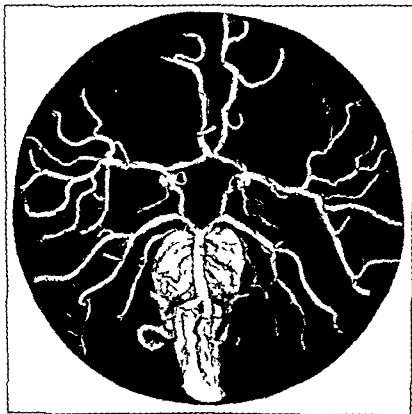


FIG 378 —The circle of Willis. The vertebral arteries are on the ventral surface of the medulla and unite to form the basilar artery on the ventral surface of the pons The internal carotid arteries have been cut and their lumina can be seen Arising from the circle are the anterior middle and posterior cerebral arteries In this particular illustration small symmetrical aneurysms can be seen just proximal to the bifurcation of the anterior and middle cerebral arteries (Courtesy of Dr W H. Chase)

supratentorial containing the cerebrum and the subtentorial containing the cerebellum and brain stem Between the dura and the brain are the arachnoid and the pia mater which together form the leptomeninges These can be imperfectly separated from one another as trabeculae join them The arachnoid does not dip into the sulci while the pia does In addition the pia mater penetrates into the brain substance with the blood vessels about which it forms the perivascular or Virchow Robin spaces

The arterial blood supply to the brain is furnished by means of the internal carotid and the vertebral arteries The internal carotid arteries reach

the intracranial cavity through the carotid canals and the vertebrals through the foramen magnum At the base of the brain these arteries form the circle of Willis which gives off the anterior, middle, and posterior cerebral arteries (Fig 378) The cerebellum and pons are supplied by branches of the basilar artery formed by the union of the two vertebral arteries The venous blood is distributed to large sinuses in the folds of the dura and thence to the internal jugular veins which leave the skull through the jugular foramina The blood supply to the spinal cord is derived from the vertebral and intercostal arteries These form the anterior spinal and the anterior median arteries, which lie in the anterior median fissure, and give off branches to the anterior horns and for a variable distance beyond these In addition the posterior spinal arteries form branches which extend around the periphery of the cord and send terminals in at right angles to its surface

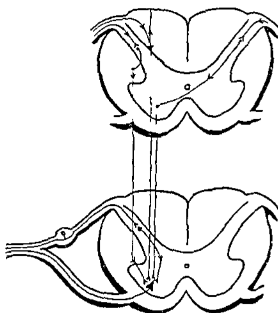


Fig 3 9—Diagram of a simple segmental reflex are ipsilateral and uptas gmental reflexes showing how several afferent pathways converge on one anterior horn cell and how spinal reflexes of different complexities may be brought about (From Grinker Neurology Courtesy of Charles C Thomas Publisher Springfield Ill)

The central nervous system regulates the adaptation of the individual to the environment, both external and internal It is not alone in this regulation as the endocrine glands partake in the same function and there is an intimate correlation between nervous and hormone action The adaptation may be a simple one such as the withdrawal of a limb from a noxious stimulus or a very complicated one such as the adjustment of the personality to an emotional situation Mechanically this adaptation is brought about through the exercise of the properties of nervous tissue irritability and conductivity Nervous tissue can be stimulated and can transmit the stimulus to a distance Transmission of the nervous impulse along the axones, although accompanied by electrical change, is not transmission of an electrical current but the analogy to an electrical current is a useful one

The simplest type of nervous action is the spontaneous discharges of energy which are shown by the wavelike change in action potential of nerve cells and fibers while at rest The simplest form of *exteriorization of nervous* function is manifested by the simple reflex Such a reflex forms an arc (Fig 379) which is made up of an afferent impulse ordinarily a sensory impulse coming into the central nervous system from the periphery and an efferent impulse usually a motor impulse going out from the central nervous system to the periphery In between the afferent and the efferent neurones there is a third an intercalated neurone The knee jerk is an example of such a reflex A tap on the patellar tendon gives rise to an impulse which travels into the spinal cord through the posterior nerve root thence to the anterior horn cells and to the periphery through their axones The result is a contraction of the quadriceps muscle of the same side and a rapid twitchlike extension of the leg at the knee joint Reflexes may vary in complexity from the theoretically possible one involving one segment of the spinal cord to the highly complicated conditioned reflexes, such as the secretion of gastric juice in response to a stimulus which has previously been associated *with the giving* of food It is possible that a great many personality reactions are built up on such a foundation of reflex action (see Chapter XVI)

THE DIAGNOSIS OF NERVOUS DISEASES

The diagnosis of nervous diseases involves the determination of the site of the lesion and the nature of the lesion These two problems the anatomical and the pathological necessitate careful history taking careful physical examination and the careful and judicious use of the special examinations which are available

The anatomical diagnosis of nervous diseases or the determination of the site of the lesion depends almost entirely on physical examination Abnormal physical signs depend upon the part that is involved and not upon the type of lesion Thus a destructive lesion of the pyramidal tract whether vascular inflammatory neoplastic or other will produce an upper motor neurone type of paralysis in the part supplied by the destroyed fibers

Lesions of the nervous system may be irritative as in epileptic discharges and fibrillary movements or destructive as in motor paralyses and sensory losses Because of the integrating character of the nervous system and the correlation of its different parts to one another a destructive lesion will do two things (1) it will abolish the function of the part it has destroyed, giving rise to paralytic phenomena and (2) it will release the remainder of the central nervous system from the inhibitory or *modifying influences* ordinarily exerted by the destroyed part and so will give rise to release phenomena These two types of physical signs are well shown in lesions of the *pyramidal* tract

The remainder of this section is devoted to the consideration of the anatomical diagnosis of nervous diseases and pathological considerations are dealt with in the following section

Disturbances of Motility

Voluntary motion is a complex function which is controlled by many areas of the central nervous system It is exteriorized through the pyramidal (cortico spinal) tract or upper motor neurones, and through the anterior horn cells and their axones or the lower motor neurones In addition, however for its useful functioning it requires to be coordinated, a function which is controlled by the cerebellum Control and maintenance of posture and of tonus are also necessary and these are made possible through the integrity of vestibular reflexes, striatal pathways and of impulses which are exteriorized through the rubrospinal and reticulospinal tracts Ordinarily in dealing with impairment of motor function one speaks of paralysis of muscles and yet this term is usually misapplied In upper motor neurone lesions for example, there is a paralysis of voluntary movement but by no means a paralysis of muscles, the reflex excitability of which may be increased

It has been said that the exteriorization of voluntary movement is brought about through the action of two neurones, the upper motor neurone and the lower motor neurone Because of this there are two types of lesions the physical manifestations of which are shown in the following comparative tabulation

	Upper Motor Neurone Lesion	Lower Motor Neurone Lesion
Nutrition	Preserved no atrophy except that of disuse	Impaired atrophy is present
Power	Diminished or lost	Diminished or lost
Tonus	Increased	Diminished
Clonus	Present	Absent
Tendon reflexes	Increased	Diminished or lost
Superficial reflexes	Abolished	Abolished
Pathological reflexes	Present	Absent
Faradic excitability	Preserved	Diminished or absent

In muscles which are undergoing atrophy due to lesions of the anterior horn cells and which are not yet fully paralyzed fibrillary movements are frequently and characteristically observed Similar fibrillations may occur with disease elsewhere in the lower motor neurone The increase in tonicity or resistance to purely passive movements in upper motor neurone lesions is usually more marked in the flexor groups of muscles Frequently at the onset of hemiplegia resulting from a lesion of the pyramidal tract tonicity will be diminished in the parts involved and the tendon reflexes will be absent but usually within forty eight hours this state will begin to pass into that characteristic of a pyramidal tract lesion The cause of the diminution in tone and absence of tendon reflexes in such a case is the widespread and sudden shock to which the entire central nervous system is subjected On the other hand there are cases of hemiplegia in which the diminution in tonicity remains At the present time it is believed that if components of the pyramidal tract arising from both area 6 and area 4 (Brodmann) of the cerebral cortex are involved, the hemiplegia will be spastic whereas if only area 6 or its axones is involved the hemiplegia will be flaccid The chief superficial reflexes that are tested are the abdominal and plantar reflexes The normal response to stroking lightly the outer border of the sole of the foot is flexion of all the toes but in

pyramidal tract lesions, or upper motor neurone lesions, a pathological reflex replaces this normal one In such cases stimulation produces extension of the big toe with or without flexion and fanning of the remaining toes (plantar extensor response or Babinski sign) This same response can be brought about and so corroborated, by other types of stimulation such as stroking the outer border of the foot (Chaddock reflex) or by forcibly running the fingers along the borders of the tibia (Oppenheim reflex) Other pathological reflexes occur which are less dependable and the presence of which cannot with certainty point to the particular location of the lesion within the central nervous system Faradic excitability of a nerve muscle preparation depends upon the integrity of the myoneural junction and in lower motor neurone lesions, after a sufficient interval (10 to 20 days) has elapsed for the axone to degenerate, this excitability is lost Galvanic excitability on the other hand is exerted directly on the muscle fibers and as long as these remain contractile it is preserved although it is altered in lower motor neurone lesions

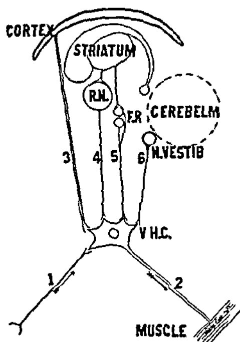


Fig 380 —Diagram of the final common path and the various levels of the nervous system acting upon it R N red nucleus F R formatio reticularis V H C ventral horn cell 1 simple reflex arc 2 the final common path 3 the corticospinal or pyramidal tract 4 the rubrospinal tract 5 the reticulospinal tract 6 the vestibulospinal tract. (From Lennox and Cobb Epilepsy Williams and Wilkins Company Baltimore)

In further considering the physical manifestations outlined in the above table several striking features are noted In the first place a lower motor neurone lesion diminishes or abolishes all of the functions recorded On the other hand in upper motor neurone lesions some functions are diminished or lost (power superficial reflexes) some are preserved (nutrition faradic excitability), some are increased (tonus tendon reflexes) and some new things make their appearance (pathological reflexes clonus) This is easy to understand when one recalls that the lower motor neurone is the final common

pathway of transmission of motility and its correlated phenomena to the periphery and so a lesion of this final common pathway will prevent the exteriorization of all the modalities of function which are transmitted to the anterior horn cells and conducted along their axones (Fig 380) The upper motor neurone, however, is not a final common path Its impulses are exerted on the anterior horn cell which receives in addition impulses from many other pathways, such as the rubrospinal reticulospinal and vestibulospinal tracts and also the pathways for reflex action which exist within the cord itself As a result of this a lesion of the pyramidal tract will cause abolition of the function being transmitted along the pyramidal pathway but it will leave the lower motor neurone free to exteriorize functions being transmitted to it by other pathways Furthermore these functions are no longer subjected to the inhibitory influences which the pyramidal tract normally places upon them and so may be increased or otherwise altered

The anatomical diagnosis in cases of disturbance of motility depends not only on the determination of what pathway is involved but also upon where in its course it is involved The pyramidal tract arises from the large pyramidal (Betz) cells in the pre Rolandic area The axones of these cells converge as they pass downward between the basal ganglia where they form the internal capsule and then descend into the medulla as compact and circumscribed bundles As it passes through the midbrain, pons and medulla this tract gives off its cranial nerve components which cross to the cranial nerve nuclei of the opposite side When the tract reaches the lower medulla it crosses almost completely and descends in the opposite side of the spinal cord Those fibers which do not cross but descend the homolateral side of the cord do not concern us in a text of this kind Having reached the segment of the cord which supplies the part to which they are conveying function the fibers synapse with the anterior horn cells or cells of the lower motor neurones The axones of the latter which, as was noted above are subjected to influences from several pathways, then transmit the impulse to the periphery It is apparent therefore that the pyramidal tract arising in one hemisphere of the brain carries impulses to the opposite side of the body whereas the lower motor neurone arises from the same side of the cord as that of the body to which it is distributed Furthermore the lower motor neurone is strictly a segmental structure, whereas the pyramidal tract is not In the motor cortex the fibers which are to supply the leg arise uppermost those for the arm and trunk are in the middle, and those for the face tongue and jaw are at the lower end of the pre Rolandic convolution

In the accompanying diagram (Fig 381) destructive lesions have been marked at different levels to indicate characteristic types of syndromes As the consideration of irritative phenomena of the cerebral cortex is particularly applicable to the discussion of the cerebral cortex and of the epilepsies it has been reserved for those sections (pages 1006 *et seq* and 1152)

Lesion 1 is located in the pre Rolandic cortex and immediately subcortical Because of its size it involves the fibers only to one limb and so will cause a monoplegia of the upper motor neurone type If it is located high up

in the motor cortex, as illustrated, the paralysis will be in the leg, if it is situated lower down, about the middle of the motor area the paralysis will be in the arm, while if it is in the lowest part of the motor convolution the paralysis will be in the face and adjacent structures In each case the paralysis will be contralateral, that is, on the opposite side of the body to that of the brain in which the lesion is located

Lesion 2 is of approximately the same size, but is situated in the internal capsule where the corticospinal fibers have converged as they pass downward Resulting from it there will be a hemiplegia of the opposite side of the body with an upper motor neurone type of paralysis of the face, arm and leg Other cranial nerves such as the oculomotor and hypoglossal may also be involved

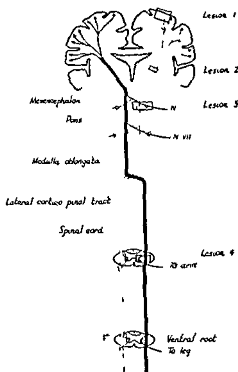


Fig 381 —A diagrammatic representation of lesions at different levels in the upper and lower motor neurones Resulting symptoms are described in the text (Modified from Ranson The Anatomy of the Nervous System W B Saunders Company)

Lesion 3 explains anatomically the crossed paralyses in which a cranial nerve is paralyzed on the same side as the lesion and the arm and leg on the opposite side of the body The various combinations have been given the names of the observers who first described them but the important thing is that each combination is due to a lesion situated at the level of origin of the cranial nerve involved on the same side Thus a lesion on one side of the midbrain at the level of origin of the oculomotor nerve and involving it and the pyramidal tract will cause a homolateral oculomotor paralysis and a contralateral paralysis of arm and leg Similarly a lesion in the pons will cause

a homolateral facial paralysis and a contralateral paralysis of arm and leg

Lesion 4 is in the cervicothoracic enlargement, made up of the segments of the cord supplying the upper extremity The lesion involves the lower motor neurones to the arm and the upper motor neurones for the body seg ments below the arm The result will be a flaccid, atrophic, lower motor neurone

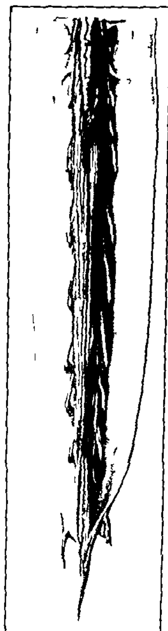


Fig 382 —The lumbo acral cord and cauda equina (El berg Am J M Sc Philadelphia 191)

type of paralysis in the arm absent abdominal reflexes, and a spastic upper motor neurone paralysis of the leg with increased tendon jerks and plantar extension (Babinski sign) following stimulation of the sole of the foot All the physical signs will be homolateral that is on the same side as the lesion because the pyramidal tract is involved in the cord after it has crossed in the

medulla If the lesion is too small to involve all the lower motor neurones to the arm the flaccid paralysis will be confined to the distribution of those that are involved

At birth the spinal cord fills the vertebral canal and each mixed nerve made up of anterior and posterior nerve roots passes horizontally through the inter vertebral foramen at its own level As growth progresses the vertebral column increases greatly in length whereas the spinal cord does not The spinal nerves passing through the intervertebral foramina are consequently pulled out of their original position by the growing vertebral column and instead of passing hori zontally out of the vertebral canal descend within the canal until they reach their own foramina This descent is not present in the upper spinal nerves in the cervical region, because at that level the growth is not disproportionate but at progressively lower segments of the vertebral column the disproportion be comes progressively more marked and the segment of the cord no longer lies opposite its corresponding vertebra In adult life the spinal cord ends op posite the first lumbar interspace and all the spinal nerves which are to leave through lower intervertebral foramina must descend below the termination of the cord The mass of lumbar and sacral nerves which thus pass downward in the vertebral canal forms the cauda equina (Fig 382) which contains both motor and sensory fibers The motor fibers in the cauda equina are therefore all axones of anterior horn cells and so all lower motor neurone structures Motor paralyses following cauda equina lesions are consequently of the lower motor neurone type

Electrical stimulation of the precentral cortex produces focal movements of single muscles or of a very restricted number of muscles and not fully developed purposive action It is obvious that higher centers of initiation and elaboration of combined muscle movement must exist within the brain centers which build the individual muscle components into the complex pat tern which volition dictates Very little is known of these centers The frontal adversive field situated in the posterior part of the first and second frontal convolutions is one such area and stimulation of this produces turn ing of head and eyes to the opposite side while destruction produces head and eye turning to the same side Not only must all the components of complex purposive movements be set in action but their action must also be synergized or coordinated and this is accomplished through the action of the cerebellum

The cerebellum has two hemispheres which are joined by the vermis The cortex is made up of three layers of cells and within the cerebellum itself are several grey nuclear masses the largest of which is the dentate nucleus Con nection with the brain stem is made by three pairs of peduncles the superior or brachium conjunctivum the middle or brachium pontis and the inferior or corpus restiforme Through the inferior cerebellar peduncle afferent impulses enter the cerebellum from the dorsal spinocerebellar tract the nuclei of Goll and Burdach the vestibular nucleus and the inferior olives Through the middle cerebellar peduncle fibers from the opposite pontine nuclei enter These are fibers of the corticopontocerebellar system from the cortex of the frontal and temporal lobes particularly The superior cerebellar peduncle is an efferent structure made up chiefly of fibers from the dentate

nucleus of one cerebellar hemisphere to the opposite red nucleus and thalamus From the red nucleus arises the rubrospinal tract which crosses at once and descends into the spinal cord Efferent cerebellar impulses therefore cross from one cerebellar hemisphere to the opposite red nucleus and then, by means of the rubrospinal tract, back to the homolateral side of the spinal cord Afferent fibers of the ventral spinocerebellar tract, from the homolateral side of the spinal cord enter the cerebellum in close contact with the brachium conjunctivum Consequently the connections of the cerebellum proximal to itself are chiefly with the opposite side of the brain and the connections distal to itself are chiefly with the same side of the cord

Since the cerebellum is a coordinating center, destruction of it impairs coordination and leads to ataxia and dysynergia The incoordination is manifested on the same side of the body as the side of the cerebellum involved, and can be tested for by having the patient carry out any movement which requires muscular coordination Walshe has described the symptomatology as *follows* (1) *abnormalities of resting muscle—loss of tone*, (2) *abnormalities* of muscular contraction—excessive range and force of contraction, intermittent and unsteady contraction, premature relaxation, extreme readiness of fatigue (3) abnormalities of voluntary movements—faulty functional combination of the muscles engaged in a voluntary movement, (4) the effect of voluntary efforts at correction

Clinically the following abnormal signs occur There is nystagmus when the eyes look laterally toward the side of the lesion Speech is ataxic, slurred and jerky There is incoordination, especially in fine movements such as touching the nose with the finger, touching the finger of the examiner, rapid tapping of the finger on a table, rapid alternate pronation and supination of the forearm (dysdiadokokinesia), placing the heel of one foot on the opposite knee etc The ability to carry out movements accurately is lost, if the patient attempts to reach for an object he will overshoot the mark or fall short of it and his attempts to correct this will result in clumsy, inaccurate movements There is also difficulty in stopping movements when they should be stopped, for example, if forcible flexion of the patient's forearm is prevented by the examiner s hand and if the latter is suddenly removed, the patient's forearm will not relax in time and will rebound forcibly The gait is also disturbed and the patient tends to sway or stagger or fall toward the side of the lesion In some cases in an effort to overcome this deviation from a straight line, the patient s body will turn slightly away from the side of the lesion while the head turns slightly toward the side of the lesion Tremor frequently occurs and it is a tremor which becomes coarser and more marked on voluntary movements (intention ' tremor) or may be present only at such times As noted in Walshe s description of the symptomatology there is usually some diminution in muscle tonus on the side of the lesion and sometimes because of the impairment described above, voluntary power will be slightly diminished With these changes the knee jerk sometimes becomes pendular in type and the unsupported leg will swing backward and forward after the knee jerk has been elicited

The maintenance of tone depends upon the integrity of the segmental reflex arcs, and for that reason when the lower motor neurone, or the efferent pathway of the arc, is destroyed, tonicity is abolished In addition, however, higher centers modify the degree and distribution of the tonus It has been stated that in pyramidal tract lesions tonicity is increased and this increase is primarily a flexor increase in the arm In cerebellar disease tonicity is diminished In disease of the extrapyramidal motor system the striatal rubral and reticular pathways, tonicity is also increased, but the increase is general and *not selective as that of the pyramidal cases Furthermore in extrapyramidal* disease, increased tonicity is of the "cog wheel" character, and passive movement of the limb reveals not a constant increase in tone but a succession of hypertonicity and relaxation

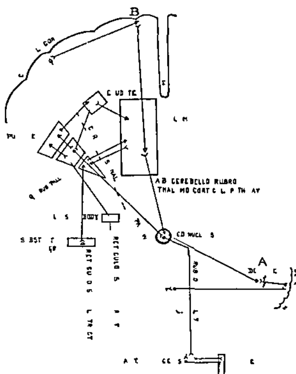


Fig 383 —A diagrammatic representation of the extrapyramidal pathways (From Young Involuntary Movement Courtesy of Canad M A J 1934)

The maintenance of posture and the righting reflexes of the body are subserved by mechanisms associated with extrapyramidal pathways and with reflexes set in action by afferent impulses arising from the eyes body neck and labyrinth Exteriorization of function is brought about by vestibulospinal rubrospinal and reticulospinal pathways The discussion of decerebrate rigidity, and of paraplegia in flexion and in extension is postponed until the end of this section

The extrapyramidal pathways are efferent systems of the corpus striatum the red nucleus the reticular nuclei and the vestibular nucleus of Deiter The last forms a vestibulospinal tract concerned with reflex responses to stim

ulation of the semicircular canals by changes in posture of the head The remainder of these pathways are represented in Fig. 383 It will be seen from this that the systems are largely split up into relays and that they exteriorize function arising in the basal ganglia, the cerebellum and various hypothalamic diencephalic and mesencephalic nuclei The anatomical connections of these various paths have not yet been fully determined

Disease of these extrapyramidal pathways results in disturbances of tonicity and the appearance of abnormal movements The abnormal movements are tremors chorea athetosis and dystonic movements While attempts have been made to explain each particular type of abnormal movement on disease of a particular nucleus of this system they are unwarranted at present It is possible, and indeed likely, that the pathogenesis is based not upon disease of one nucleus or path only but of the complex connections between the cerebral hemispheres cerebellum and extrapyramidal motor nuclei Experimentally it has not been possible to reproduce these symptoms

Choreic movements are rapid irregular hypotonic objectively purposeless but subjectively purposeful movements which may involve any part of the body They may be confined to the face one limb one side or be generalized They are separate abrupt irregular and of short duration They may consist of fine movements such as of the fingers or tongue or of violent constant movements sufficient to throw the patient out of bed Further characteristics are described in the section on Chorea (Chapter III) Athetosis like chorea may involve any part of the body and frequently occurs after infantile hemiplegia which has partially recovered The movements are slower, more grotesque, and may be brought on by voluntary movement of the affected limb or the opposite one They are frequently forcible extensor or flexor movements of hands or fingers feet or toes associated with marked increase in muscular tonicity Slow tortuous movements of the arms away from the body also occur The movements of dystonia musculorum or torsion spasm resemble athetosis in many ways but are usually more widespread involving at first a whole segment of the body and perhaps later the entire body which is twisted forcibly into bizarre patterns These movements are impossible to describe accurately but once seen will not be forgotten The tremor of extrapyramidal disease is unlike that which occurs in lesions of the cerebellum and its superior peduncle In the former the tremor which may be of the 'pill rolling' variety is present at rest and usually disappears when voluntary movements are made while in the latter the tremor is induced or increased by voluntary movements the so called 'intention tremor' At times it is difficult to separate these two types All these movements are release phenomena and they are abolished if the upper or lower motor neurone is completely destroyed because their exteriorization is brought about through these systems

Somatic Sensibility

Somatic sensibility is conveyed to the central nervous system by sensory fibers which enter the cord through the posterior nerve roots The cells of these fibers are situated in the posterior root ganglia which are outside the central nervous system itself and which have developed from the ectodermal

neural crest Many types of cells have been described in these ganglia and the sensory fibers themselves have been subdivided according to whether or not they are myelinated and, if so according to how heavily myelinated they are Not only do the fibers carrying different types of sensibility have different thicknesses of myelin covering them, but they also have different conduction rates The types of sensibility entering the spinal cord from skeletal structures are touch pain, position (muscle and joint sense) and vibration

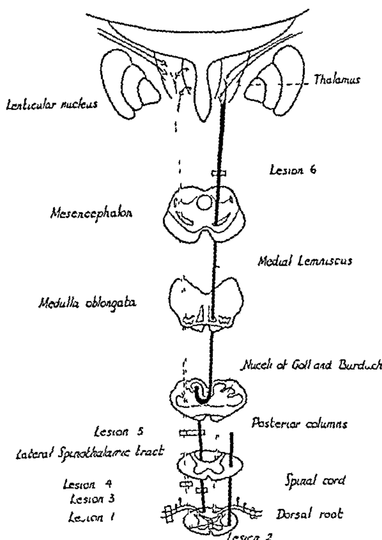


Fig 384—A diagrammatic representation of the sensory pathways Those from one side of the body are in solid line and those from the other side in broken line Lesions have been marked at different levels and are explained in the text (Modified from Ranson Anatomy of the Nervous System W B Saunders Company)

After entering the cord the fibers carrying position and vibration sensibility ascend the homolateral columns of Goll and Burdach (posterior columns) to the medulla where they enter the nuclei of Goll and Burdach New neurones there pick up the function and their axones cross to the medial lemniscus of the opposite side and terminate in the ventral nucleus of the thalamus Some

of the fibers from the nuclei of Goll and Burdach terminate in other nuclear structures in the midbrain and diencephalon, but these connections have not been fully established

The fibers conveying pain and temperature sensibility end in the grey matter immediately on entering the cord New fibers then convey function across the midline, anterior to the central canal of the cord, to the opposite spinothalamic tract The crossing takes place at the level at which the corre sponding fibers have entered the cord or within one or two segments above that The fibers of the spinothalamic tract ascend in the cord and brain stem and also terminate in the ventral nucleus of the thalamus Many of the fibers of the spinothalamic tract terminate before reaching the thalamus, but again the anatomical details of these are obscure Within the thalamus there are intimate connections between the various nuclei, and from the thalamus sen sation is conveyed to the cerebral cortex by fibers which pass through the internal capsule posterior to the descending pyramidal tract fibers Most of these corticipetal axones terminate in the post Rolandic convolution but some go to the pre Rolandic convolution and others to the parietal cortex Touch sensibility is transmitted upward by both spinothalamic and posterior column systems Consequently sensation from each half of the body ascends in both sides of the spinal cord but eventually all sensation which is to reach con sciousness from one half of the body is distributed to the opposite cerebral hemisphere

From a knowledge of these anatomical details one can determine the location of lesions which produce sensory disturbances in the periphery (Fig 384) In the first place, a lesion in a segmental structure the nerve root or the crossing fiber to the spinothalamic tract, will produce signs within the seg mental distribution only whereas a lesion of the posterior columns or spino thalamic tract will produce sensory disturbances at all levels below the lesion as these tracts are transmitting sensation from all the segments Second the type of sensory impairment will depend upon the fibers involved Again a diagrammatic representation of lesions is used in explanation

Lesion 1 is in the peripheral nerve or the posterior nerve root and the sensory loss resulting will involve all forms of somatic sensibility in the seg mental distribution of the fibers involved The segmental distribution of the posterior nerve roots and spinal cord segments is discussed later

Lesion 2 is in the commissural fibers, carrying pain and temperature sen sibility from one posterior grey horn to the opposite spinothalamic tract so the sensory loss will again be of segmental distribution From the foregoing explanation the anesthesia should be for pain and temperature sensibility but clinically a dissociation of these two types of sensibility may be found for example temperature sensibility may be lost and pain sensibility preserved as so often happens in typical syringomyelia

Lesion 3 is in the posterior columns of one side and will abolish vibration and position sense and two point discrimination on the same side of the body up to the level of the lesion The patient will not be able to perceive or ap

preciate passive changes in the position of muscles and joints in the involved area nor the vibration of a tuning fork placed over a bony point in that area In addition it will require a wider separation than normal of two points in order that they may be appreciated as two rather than as one Of course as in all neurological conditions function may not be completely abolished but *only reduced if the destruction of the pathway is not complete*

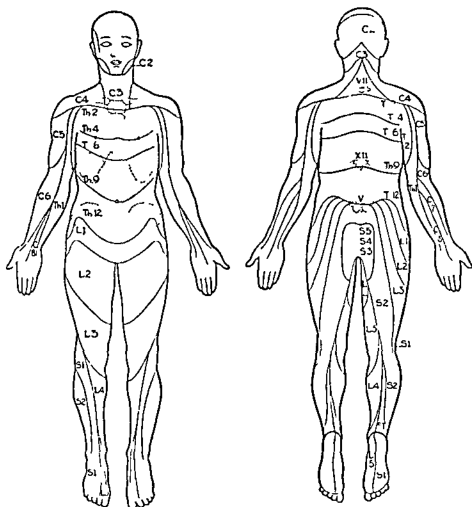


Fig 38 —Diagrams to show the segmental distribution of the spinal cord segments and nerve roots (Elsberg)

Lesion 4 is in the spinothalamic tract on one side and will abolish pain and temperature sensibility on the opposite side of the body up to the level of the lesion Because of the fact that fibers to the spinothalamic tract from progressively higher levels push those from lower levels toward the periphery of the cord it sometimes happens that in intramedullary lesions or lesions within the spinal cord which cause a loss of pain and temperature sensibility up to the level of the lesion sensory fibers from the distribution of the sacral segments will escape and sensation which they are transmitting will be preserved

of the fibers from the nuclei of Goll and Burdach terminate in other nuclear structures in the midbrain and diencephalon, but these connections have not been fully established

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becomes hyperemic, its edges become blurred and swollen the veins become turgid and tortuous and exudate may obliterate some of the vessels The degree of swelling may be measured by means of the lenses on the ophthalmoscope and so the progress or recession of the swelling can be accurately followed After a long continued swelling of this type the nerve may undergo secondary atrophy, the exudate organizes, the disc becomes greyish white in color the vascular supply diminishes and the margins remain indistinct

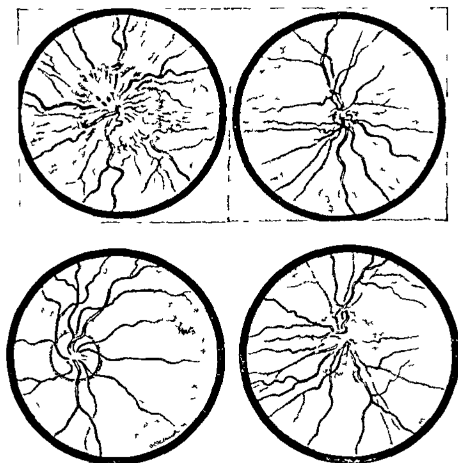


Fig 386—Above on the right a beginning choked disc on the left a highly choked disc with hemorrhage Below on the right secondary optic atrophy on the left primary optic atrophy (From Grinker Neurology Courtesy of Charles C Thomas Publisher Springfield Ill)

In contradistinction to secondary optic atrophy following papilledema due to increased intracranial pressure primary optic atrophy follows direct involvement of the nerve in disease particularly in tumors tabes dorsalis and disseminated sclerosis In primary atrophy the disc becomes white the margins are very sharply delimited and the vascularity diminishes In addition to swelling and atrophy of the disc the retina may show characteristic changes in arteriosclerosis diabetes nephritis miliary tuberculosis and hemorrhagic diseases so that the value of ophthalmoscopy is not confined to the diagnosis of nervous diseases

Lesion 5 is a combination of the last two and involves the spinothalamic tract and the posterior columns on the same side of the cord This will result in a homolateral loss of *position and vibration sensibility and a contralateral* loss of pain and temperature sensibility both up to the level of the lesion

Lesion 6 involves the medial lemniscus of one side and so interrupts fibers from the opposite nuclei of Goll and Burdach The result will be a loss of *position and vibration sense on the opposite side of the body*

The segmental distribution of the spinal cord is represented in Fig 385 The diagrams compiled by different observers vary but little and agree in most details It will be seen that the lowest segmental distribution, that of the *third fourth, and fifth* sacral segments and roots, supplies a saddle shaped area around the anus and the genitals and perineum The second sacral supplies a narrow strip up the back of the leg the first lumbar supplies the region of Poupart's ligament the seventh thoracic or dorsal segment supplies the level of the xiphisternum Although the representation over the limbs especially the legs, may not appear to be segmental, it is truly segmental from a developmental standpoint, as the limb buds, which have pulled out their nerve supply with them undergo some rotation It will be noted from the chart that if sensation is lost on the body up to the level of the second rib, it is necessary then to examine the segments distributed to the arms and hands to determine whether or not higher segments are involved The accurate localization of lesions involving the spinal cord depends upon a knowledge of the pathways that are involved and also upon the segmental distribution as *illustrated in* the figure, so that the level of involvement may be determined

The Cranial Nerves

The cranial nerves are twelve in number on each side *They are* either motor or sensory or mixed, and they pass from the base of the brain through foramina in the skull to and from the parts which they innervate

The first or olfactory nerve carries sense of smell from the mucous membrane *of the nose where the fine filaments to the olfactory bulb arise* Impairment of sense of smell is usually due to local causes in the nose, but in the case of tumors on the ventral surface of the frontal lobe in the olfactory groove anosmia may occur and may be a localizing sign of value Hallucinations of *smell are sometimes present in temporal lobe tumors* as a result of irritation of the olfactory cortex in the uncinate gyrus This usually occurs as a paroxysmal discharge which is part of a focal epileptic attack and is often associated with other phenomena especially auditory or visual The hallucination is most frequently a disagreeable one

The second cranial nerve or the optic nerve is the special sensory nerve from the retina Testing of its function forms one of the most important parts of a neurological examination and may show signs of extreme value from the standpoint of both anatomical and pathological diagnosis In the first place the fibers of this nerve can be seen on ophthalmoscopic examination, and when intracranial pressure becomes increased the nerve head or optic disc becomes visibly swollen and edematous Normally this optic disc (Fig 386) is a sharply outlined yellowish white circular area but when swollen it

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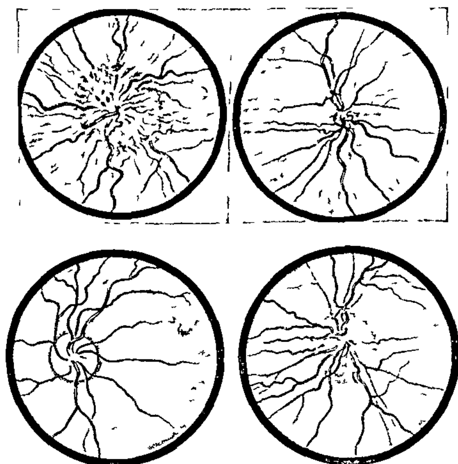


Fig. 356.—Above, on the right, a beginning choked disc; on the left, a highly choked disc with hemorrhage. Below, on the right, secondary optic atrophy; on the left, primary optic atrophy. (From Grinker: Neurology. Courtesy of Charles C Thomas, Publisher, Springfield, Ill.)

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the anterior corpora quadrigemina, but these are concerned with reflexes and not with visual perception Because of its long and partially crossing course interruption of the visual pathway at various locations will produce characteristic defects in the fields of vision

These defects are represented in Fig 387 in which hypothetical lesions have been placed at different points and the field defects corresponding to each lesion have been charted A lesion of the optic nerve (A) causes blindness in the homolateral eye a lesion in the chiasm (*B*) if complete, as occurs characteristically in tumors of the pituitary gland causes a bitemporal hemianopsia while if the involvement of the chiasm is not complete (*C*) the defect will vary in distribution Lesions in the optic tract (from the optic chiasm to

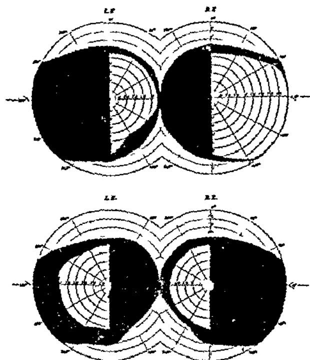


Fig 388 — Above left homonymous hemianopia with splitting of central vision Below right homonymous hemianopia with preservation of central or macular vision (From Penfield Evans and MacMillan Visual Pathways in Man with Particular Reference to Macular Representation Arch Neurol & Psychiat Apr 193[illegible])

the external geniculate body) and in the optic radiation (from the external geniculate body to the calcarine cortex in the occipital lobe) will produce a contralateral homonymous hemianopsia as indicated Quadrantic defects follow lesions (*E* and *F*) involving only part of and not the entire, optic radiation

With lesions of the optic nerve or optic tract resulting in complete blindness of the entire field (A) or part of the field (*B* *C* and *D*) the pupillary light reflex (described later) cannot be obtained from the blind part of the retina To determine the absence of this requires special apparatus which will project a light on a restricted portion of the retina and this test is rarely performed With these lesions also macular or central vision is split or hemianopic like the remainder of the field

Acuity of vision is usually diminished when papilledema or swelling of the optic disc is present, but the impairment may be greatly out of proportion to the swelling and may consist only of an enlargement of the physiological blind spot. With progressive optic atrophy, either primary or secondary, diminished acuity goes on to blindness. In the amauroses and amblyopias of toxic or other origin acuity is also diminished.

Examination of the fields of vision is particularly valuable from a localizing standpoint. The retinal fibers which form the optic nerve undergo a partial crossing in the optic chiasm. Fibers from the nasal half of each retina

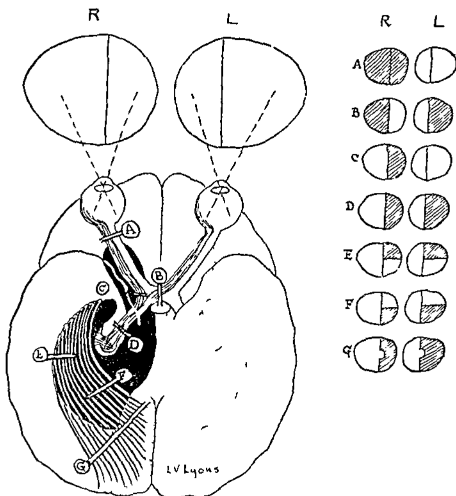


Fig. 38[illegible].—Diagram of the visual pathways and the visual field [illegible] resulting from [illegible] in various parts. (Modified from Homan.) *A*. Lesion of right optic nerve—blindness [illegible] right eye. *B*. Lesion of the [illegible] of the optic chiasm—bitemporal hemianopia. *C*. Lesion of the outer part of the optic chiasm on the right—blindness [illegible] of right nasal field. *D*. Lesion of the right optic tract—left homonymous hemianopia. *E*. Partial lesion of right optic radiation (temporal loop) in temporal lobe—upper left quadrantic hemianopia. *F*. Partial lesion of right optic radiation—producing [illegible] left quadrant [illegible]. *G*. Large lesion of right optic radiation in the right occipital lobe—producing left homonymous hemianopia with macular sparing. (From Brock: The Basis of Clinical Neurology, William Wood & Company, Baltimore, 193[illegible].)

cross while those from the temporal halves do not (Fig. 387). The optic tract so formed on each side terminates in the external geniculate body. New neurones there take up the function and carry the visual perceptions to the striate or calcarine cortex in the occipital lobe. Apart from the fibers of the optic tract which terminate in the external geniculate body, others go to

of the occipital lobes are fused into a perception of a single object Furthermore the object is perceived in three dimensions length, breadth and thickness our vision is stereoscopic If however due to the paralysis of an external ocular muscle a strabismus or squint is present then the two images will remain separate in consciousness and the object will be seen double The spatial relationship of the false and the true image will depend upon the muscle paralyzed and consequently the direction of the strabismus Furthermore the distance between the false and the true image will increase as the eyes move in the direction of the pull normally exerted by the paralyzed muscle This is easy to prove by looking at an object and then passively pushing one eyeball out of position when the object will be seen double The reason for this is that the two images of the object do not fall on similar or corresponding points of the retinae to allow their fusion

While paralysis of external ocular muscles is usually of localizing value sixth nerve paralysis alone either on one side or both, occurs frequently in increased intracranial pressure without indicating the location of the lesion The intracranial course of the sixth nerve is long and its liability to paralysis when general pressure within the skull is increased is due either to a pull upon the nerve or to compression of it by the posterior cerebral artery When the paralysis is due to a focal lesion there are usually other signs with it such as involvement of the seventh or other cranial nerves or disturbances of conjugate eye movements (see below)

Apart from the paralyses of individual movements of the eyes paralysis of conjugate movements may occur The centers for conjugate movements are not fully known those for lateral conjugate movement are supposed to be in the vicinity of the sixth nerve nuclei and those for upward and downward movement in the midbrain perhaps in the anterior corpora quadrigemina These are lower motor neurone centers and when they are destroyed conjugate movement (or movement together) of the eyes both voluntarily and reflexly is abolished Upper motor neurone centers exist but are mostly unknown The frontal adversive field (see p 1007) is an upper motor neurone center for lateral movements and stimulation of it causes forced conjugate deviation toward the opposite side Paralysis of this center causes forced deviation toward the side of the lesion because of the unopposed action of the opposite center In the same way stimulation of the cortex in the region of the angular gyrus will cause conjugate eye movements to the opposite side In paralysis of voluntary conjugate movement following an upper motor neurone lesion, reflex conjugate movement is still possible and if the eyes are fixed upon an object and the head then turned passively the eyes will remain fixed upon the object even though this necessitates conjugate deviation in a direction in which it cannot be carried out voluntarily In addition though conjugate movement in a certain direction is impossible individual movement of each eye in the same direction can be carried out The posterior longitudinal bundles which extend from the midbrain down into the cervical cord and which connect up the nuclei of the third fourth and sixth nerves the vestibular nuclei and certain nuclei in the pons is the anatomical pathway

When the lesion causing the blindness is in the optic radiation, however, primary changes do not occur in the fundus and the light reflex is not lost as the lesion does not involve the reflex arc If the lesion in the optic radiation is close to the external geniculate body, macular vision is split (Fig 388) but if it is more posterior, macular vision is preserved and the hemianopsia does not include macular or central vision All these defects are predicated upon destruction of the entire pathway concerned but disease may pick out only part of the pathway and the result may be a quadrantic rather than a complete hemianopic defect

An interesting point of differentiation between homonymous hemianopia following a lesion of the optic radiation and one following a lesion of the occipital cortex is that in the former the patient will be aware of a blank or blind area within his field, while in the latter there may be no such subjective defect except that objects in that area cannot be seen

The macula is a point on the retina horizontally level with the disc and about two disc diameters to the temporal side of it It is visible on opthalmoscopic examination as a minute bright area which is avascular and surrounded by an area of duller red than the remainder of the retina It is the point of greatest visual acuity and it is to bring light rays upon it that we look directly at objects and converge as we look at near objects The preservation of the entire macular vision in lesions of the optic radiations has not yet been satisfactorily explained

The third, fourth and sixth cranial nerves, or the oculomotor trochlear and abducens innervate the external ocular muscles and bring about eye movements In addition the third nerve supplies the levator palpebrae superioris, which raises the upper eyelid, and also the constrictor muscle of the pupil The third nerve supplies all the muscles for movement of the eye except the superior oblique which is supplied by the trochlear nerve, and the external rectus which is supplied by the abducens nerve Impairment of extraocular movements causes strabismus and diplopia The strabismus, or deviation of the eyeball from the normal position, is brought about through the unopposed action of the muscles which are intact and may not be observable with early or partial weakness If the sixth nerve of one side is destroyed the external rectus muscle of the corresponding eye will be paralyzed the eye will be turned inward or toward the nose (internal strabismus) and outward or lateral movement of the eye will not be possible If the entire third nerve is destroyed there will be a droop of the eyelid from paralysis of the levator palpebrae superioris a dilatation of the pupil from paralysis of the constrictor muscle of the pupil an external strabismus from the unopposed action of the intact sixth nerve and diplopia Because the third nerve nucleus is a long one, which is subdivided into smaller nuclei concerned with the individual functions, involvement of it within the midbrain is usually incomplete and so only some of the muscles are paralyzed such as the levator palpebrae superioris or the constrictor muscle of the pupil Isolated lesions of the fourth nerve are rare

Because of the frontal position of our two eyes images of objects at which we look fall on both retinae and yet the two images carried in to the cortex

cause of the distribution of fibers in the pons medulla and upper cervical cord, such impairment may result from lesions over a widespread area Irritative lesions may also occur in one or more of the divisions and give rise to *the condition known as trigeminal neuralgia or tic douloureux*

The motor nucleus of the fifth nerve also lies in the pons and the fibers supply the temporal masseter and pterygoid muscles Paralysis of temporal and masseter muscles can be felt when the patient tightly clenches the teeth as the involved muscles will not contract Paralysis of the pterygoid will cause the jaw to deviate toward the paralyzed side when the mouth is opened The reason that the deviation of the jaw is to the paralyzed side is that opening *of the mouth is an active movement* not a passive droop and the unopposed action of the intact muscles forces the jaw over to the paralyzed side

The seventh or facial nerve arises in the pons and after looping about the nucleus of the sixth nerve leaves the brain stem medial to the eighth nerve It supplies all the facial muscles except those of mastication and the levator *palpebrae superioris* and also *innervates the platysma and the stapedius muscles* In addition it affords passage to parasympathetic fibers through the great superficial petrosal nerve and carries sensory impulses through the nervous intermedius and taste from the anterior two thirds of the tongue by the chorda tympani

There are two types of *facial palsy a peripheral or lower motor neurone* paralysis or Bell s palsy and a central or supranuclear or upper motor neurone paralysis In the former all the facial muscles of expression are paralyzed on the side of the lesion The forehead cannot be wrinkled the palpebral fissure is wide and gaping and the lower eyelid falls loosely away *from the eyeball so that tears which cannot reach the punctum lacrimale stream down* over the cheek The eye cannot be closed because of paralysis of the orbicularis oculi and in an effort to close it the eyeball rolls upward to expose a large area of sclera The nasolabial fold is obliterated the corner of the mouth droops and cannot be elevated Whistling is impossible and because of paralysis of the buccinator muscle food collects between the teeth and cheek and is only with difficulty dislodged If the lesion is sufficiently proximal to interrupt the fibers to the stapedius muscle and those of the chorda tympani there *will be* hyperacusis and a *loss of taste* sensibility over the anterior two thirds of the tongue If such a peripheral lesion is complete the reaction of degeneration will be found in the muscles involved after an interval of twelve to sixteen days and faradic excitability will be lost The presence of faradic response after such an interval is of good prognostic significance since it indicates that the lesion did *not cause complete destruction* of the nerve

In the supranuclear type of facial palsy the disability is contralateral and is not as widespread nor as striking because bilateral innervation of the muscles allows some preservation of function In this type of lesion the forehead muscles escape and the orbicularis oculi almost always *does* If the orbicularis oculi is weakened it is only slightly so The paralysis is practically confined to the corner of the mouth and even there the disability and

by which the action of these nuclei can be synchronized and made to work together in functional patterns

It has been stated above that the constrictor muscle of the pupil is supplied by the oculomotor nerve, this supply is by parasympathetic fibers Dilation of the pupil is brought about by sympathetic fibers from the cervical sympathetic chain The pupils constrict when exposed to light (light reflex) and dilate in darkness and they also constrict on looking at a near object (accommodation reflex) In addition to the constriction of the pupil on looking at a near object the eyes converge so as to project the image on to the macula of each eye In certain diseases of the central nervous system, notably syphilis, the reaction to light is abolished, and that to accommodation retained This is the chief feature of the Argyll Robertson pupil which is further discussed under the heading of Syphilis of the Nervous System Why this dissociation of reflexes occurs is not exactly known, but it may be due to a predilection for the disease to involve only those fibers of the optic nerve concerned in the light reflex, or to the involvement of midbrain centers, such as the Edinger Westphal nucleus concerned only with the reflex to light and not with that to accommodation A condition which may be confused with Argyll Robertson pupils is that of tonic pupils (Adie's syndrome), in which the reaction to light is extremely slow, so slow in fact that it may be thought to be absent It is frequently associated with absence of tendon reflexes which makes its resemblance to tabes dorsalis more confusing The significance of this is not known but it seems to be unimportant from the standpoint of health

The fifth cranial nerve, or the trigeminal, is sensory to the face and motor to the muscles of mastication The sensory fibers are collected into three branches, the superior or first or ophthalmic, the middle or second or maxillary and the inferior or third or mandibular These three branches unite in the Gasserian ganglion which lies on the floor of the middle fossa of the skull The sensory root from this ganglion enters the pons and divides into two parts, one of which enters the sensory nucleus in the pons and the other descends to the cervical spinal cord From both the pontine nucleus and the nucleus of the descending tract of the fifth nerve fibers cross to the opposite side ascend and enter the ventral nucleus of the thalamus The first division carries sensation from the anterior part of the scalp the forehead eyelids, lacrimal glands and the conjunctiva The second division supplies the cheek upper lip and nose The third division supplies the lower lip chin and the skin over the mandible except for a small area at the angle of the jaw which is innervated by the second cervical nerve In addition the trigeminal nerve carries ordinary sensation from the mucous membrane of the mouth and nose and takes part in the formation of the nasociliary sphenopalatine otic and submaxillary ganglia of the autonomic nervous system It is also the chief sensory nerve of the dura of the brain

Sensation from the face may be impaired over the distribution of one or all of the branches of the fifth nerve in destructive lesions and when the first division is involved the corneal reflex will also be diminished or absent Be

while in nerve deafness air conduction remains greater than bone conduction, but both are reduced A vibrating tuning fork placed on the center of the forehead is normally heard equally on the two sides, as both auditory nerves pick up the vibrations transmitted to the skull (Weber test) In cases of obstructive deafness the sound of the fork is referred to the deaf ear and heard better there than on the intact side while in cases of nerve deafness the sound is referred to the good ear Irritative lesions of the cochlear division of the eighth nerve occur frequently, both in labyrinthine disease and in disease of the nerve itself In such cases tinnitus, or noises in the ears occurs Sometimes both cochlear and vestibular branches are involved and with the tinnitus there will be vertigo

Impulses arise in the vestibular portion of the eighth nerve following alterations in the rapidity and direction of flow of the endolymph in the semicircular canals induced by changes in the position of the head and irrigation of the external auditory canal with hot and cold solutions. These stimuli give rise to postural and righting reflexes concerned in the maintenance of equilibrium The vestibular fibers enter the brain stem and terminate in several large nuclei which lie in apposition to one another From these nuclei fibers go to the cerebellum the posterior longitudinal bundles the vestibulospinal tract and other nuclei in the reticular formation

Irritation of the semicircular canals by rotation of the body or irrigation of the external auditory canal normally causes vertigo nystagmus a feeling of falling and sometimes nausea and vomiting Fasill has described 26 types of rotationally induced nystagmus depending upon the position of the head during rotation and so upon the combinations of semicircular canals stimulated on the two sides A study of the responses to such turning and irrigation is often of great value in determining the integrity of vestibular connections and of influences which modify them

Nystagmus consists of rhythmic movements of the eyes which are usually made up of a slow phase and a quick phase The direction of the nystagmus is named after the quick phase although this is just a compensatory movement to overcome the slow movement which has taken place Nystagmus occurs in some ocular diseases as partial blindness paralysis of eye muscles fatigue on fixation etc It occurs also in disease of the brain other than of the vestibular mechanism such as cerebellar and brain stem lesions and is then horizontal vertical skew or diagonal Labyrinthine nystagmus is of a mixed horizontal rotary type of moderate amplitude and rapidity and of short duration Irritative lesions of the labyrinth cause a nystagmus toward the side of the lesion and in destruction of the labyrinth the nystagmus is toward the intact side For the occurrence of nystagmus only a very limited area of central nervous system is necessary an area including the vestibular nuclei and the nuclei of the third and sixth cranial nerves While this is so other areas of the central nervous system may modify it Interpretation of the various types of nystagmus is a specialized subject beyond the scope of this book and such interpretation frequently aids in the localization of nervous disease

the deformity are not so marked as in the *peripheral* cases In lesions about the thalamus, the weakness may be *present only* on emotional movement and *not on* voluntary movement, while the reverse may be the case in lesions *proximal to the thalamus*

When only partial recovery takes place in a case of *peripheral facial* palsy, or when recovery *is long delayed*, secondary contracture may take place *in the paralyzed* muscles The palpebral fissure then narrows again and the *involved* corner of the mouth may be pulled up to a level higher than that of *the intact side* Because of these contractures the patient may seem at first glance to be paralyzed on the intact side, as that corner of the mouth is *lower*, but when *voluntary* movements are attempted the imperfect movement on the *involved* side can be seen Another complication of imperfect recovery is the inability to completely dissociate one set of movements from another Thus such a patient on forcibly closing the eyes will elevate the corner of the mouth on the diseased side, or when voluntarily showing the teeth or elevating the corner of the mouth, or spontaneously laughing or smiling will partially close the corresponding eye

Facial spasms and blepharospasms occur frequently as habit spasms or tics and sometimes also as a result of disease of the extrapyramidal system The seventh nerve also carries deep pain and pressure sensibility from the face Clinically this function is seldom deranged except in some cases of atypical facial neuralgia in which the continuance of pain after section of fifth nerve fibers is attributed to irritation of sensory fibers of the seventh nerve While *this may* be so in some cases it is certainly not true in all

The eighth cranial nerve or the auditory, is made up of two divisions a cochlear concerned with hearing and a vestibular concerned with the maintenance of equilibrium The cochlear fibers enter the brain stem and, after making connections with nuclei there ascend on the two sides in the lateral lemnisci These are distributed to the posterior *corpora quadrigemina* and the internal geniculate bodies, from the latter of which new fibers go to the *transverse gyrus of Heschl* on the dorsal surface of the temporal lobe This *gyrus* is the cortical center for hearing and auditory sensations from each ear are distributed bilaterally

Impairment of hearing or deafness may follow obstructive lesions in the channels carrying sound to the nerve endings in the internal ear or lesions in the auditory nerve itself In the latter case when the deafness is slight it is for tones in the higher frequencies of sound vibrations and this can be determined by the use of a series of tuning forks or by means of the audiometer Sound vibrations reach the auditory nerve both by air conduction and by bone conduction and normally the acuity of air conduction is greater than that of bone conduction This is easily demonstrated by blocking the external auditory meatus with the finger and placing a vibrating tuning fork on the mastoid process, when the sound will be clearly heard After the sound has disappeared, if the obstructing finger is removed and the fork placed opposite the open external auditory meatus it will again be heard (Rinne test) In obstructive deafness bone conduction becomes greater than air conduction,

rather than free and distinct association systems In the introduction to this chapter the formation of gyri and convolutions and lobes separated by sulci and fissures was described

The final answer to the question as to whether the cerebral cortex acts as a whole or whether strict localization of function resides in its various parts has not been given, but it has been established that strict localization is present in certain areas notably the pre Rolandic motor cortex and the calcarine or striate cortex On the other hand there are large areas of cortex the functions of which have not been determined and which are frequently referred to as silent ' areas By the study of the response to electrical stimulation, the pattern of focal discharges in epileptic attacks and the defects following ablation of cortical areas new knowledge is slowly being added to this subject

The motor function of the pre Rolandic cortex has been described already Electrical stimulation of this area causes contraction of muscles on the opposite side of the body, and it is from the large Betz cells of this convolution that the pyramidal tract arises It has occasionally been noted that electrical stimulation of the post Rolandic convolution will also give rise to movements and much more rarely the same result has been noted on stimulation elsewhere In the motor convolution the leg is represented uppermost the arm and trunk in the middle and the face lowermost Stimulation of the frontal adversive field in the posterior part of the first and second frontal convolutions causes turning of head and eyes to the opposite side and destruction of this area causes head and eye turning to the same side Fulton and his coworkers have within the past few years published the results and conclusions from a large series of experimental lesions in the so called premotor cortex or area 6 of Brodmann They believe that ablation results in awkwardness or clumsiness especially of fine movements forced grasping, vasomotor disturbances and increased tonus and tendon jerks on the opposite side of the body The authenticity of this premotor syndrome has been questioned especially by Walshe who states that the only constant manifestation is forced grasping and that this requires an intact corpus callosum for its appearance

It has long been tacitly accepted that the frontal lobes are the centers for highest psychic functioning and that ordinarily the left frontal lobe is especially dominant It is surprising however how irregular and indefinite is the symptomatology following removal of a frontal lobe Penfield and Evans who carefully studied patients after ablation of either the right or left frontal lobe not including the area electrical stimulation of which caused movements found very little disturbance The patients showed no disturbance in micturition tone or reflexes and no forced grasping Mental functions were very well preserved and the only impairment that could be found seemed to be in the processes prerequisite for planned initiative ' It is apparent therefore that the physiology of the frontal lobe is still a matter for careful research and it is the subject of much investigation at the present time

The temporal lobe is one of the great sensory regions of the brain and in it are the cortical centers for taste smell and hearing The fibers subserving

The ninth and tenth cranial nerves, the glossopharyngeal and vagus, are closely associated and arise from common nuclei in the medulla Motor fibers arise from the nucleus ambiguus and supply the constrictors of the pharynx the muscles of the soft palate and the vocal cords Taste fibers from the posterior third of the tongue enter the nucleus solitarius, and other sensory fibers end in the dorsal vagus nucleus Sensations from the upper respiratory tract and middle ear enter the brain stem through the ninth nerve The vagus is a great parasympathetic nerve which is concerned with the function of the thoracic and abdominal viscera In bulbar palsies, which are lower motor neurone lesions of the nerve supply from the medulla there are dysarthria, dysphagia and dysphonia Glossopharyngeal neuralgia is manifested by paroxysmal pains like those of trigeminal neuralgia but situated in the throat Eustachian tube and behind the ear, and individual attacks can be induced by certain movements of the soft palate and nasopharynx

The eleventh cranial nerve or spinal accessory, arises in part from the medulla and in part from the cervical spinal cord It innervates the trapezius and the sternocleidomastoid muscles When these are paralyzed, the shoulder cannot be shrugged and the sternocleidomastoid muscle, which pulls the occiput downward and toward its own side, is also inactive

The twelfth nerve or hypoglossal, is the motor nerve to the tongue and when it is paralyzed the protruded tongue deviates to the weak side The reason for this is that protrusion of the tongue is an active movement and, if this is paralyzed on one side, the opposite overacts against no resistance and so pushes the tongue away If the paralysis is a lower motor neurone one there will be atrophy of the tongue as well and this frequently occurs in bulbar paralysis In such cases also fibrillary twitchings may be seen in the tongue In supranuclear lesions atrophy does not occur Occasionally in the normal individual the tongue tends to deviate very slightly to one side and in cases of peripheral facial palsy there may seem to be quite an appreciable deviation, but this is overcome when the mouth is pulled passively into a straight position while the tongue is protruded

The Cerebral Cortex

The cerebral cortex is made up of six layers of cells which vary in diameter from 6μ to 120μ or more Depending upon the architecture of these six layers Brodmann was able to differentiate 52 distinct cortical areas and other observers notably Economo have described more This great cellular mantle forms as far as is known the highest centers for cognitive function for emotional states and reactions and perhaps though it is not certain for consciousness itself It is the final integrating center for all sensations that reach consciousness and the highest center for the initiation of reactions that are voluntarily performed It sends fibers to lower centers (corticifugal fibers) and receives fibers from lower centers (corticipetal fibers) and by means of association fibers its various subdivisions are brought into communication with one another The largest group of such association fibers forms the corpus callosum which joins the two hemispheres, though there is some evidence to support the belief that the callosal fibers are collaterals of other systems

The study of focal epileptic discharges plays an important part in the investigation of cortical function and localization Irritative lesions such as tumors, scars, vascular abnormalities and areas of atrophy characteristically set off paroxysmal discharges which manifest themselves outwardly as Jacksonian epileptic attacks

Jacksonian epileptic attacks begin in one part, spread to contiguous parts and always follow the same pattern The part in which they begin, or the function which they disturb first, will depend upon the focus from which they arise An exact description of such an attack will usually allow a very accurate diagnosis of the site of the lesion The irritative discharge having begun will spread as ripples spread when a stone is thrown into a smooth surface of water At any time during their course these focal attacks may become generalized and they may or may not be associated with loss of consciousness which may be present from the beginning or supervene at any time during their progress

Focal epileptic attacks arising from lesions in the frontal lobe are primarily motor Usually the earliest phenomenon is a turning of the head and eyes away from the side of the lesion and then clonic convulsive movements beginning in one part and spreading to adjacent parts If the discharging focus is high up in the frontal lobe, the convulsive movements will begin in the opposite foot, then spread to the arm and then to the face If the lesion is in the vicinity of the arm motor center the movements will begin in the hand or arm and then spread to the face and the leg and the foot In the same way, if the lesion is lower in the frontal lobe the attack will begin in the face, then spread to the arm and then to the leg As noted above, the attack may at any time become bilateral and generalized and consciousness may or may not be lost at any time during the train of events

Jacksonian attacks induced by a lesion behind the Rolandic fissure, in the parietal lobe manifest themselves first by sensory phenomena which may then be followed by convulsive movements The reason is apparent as sensory cortex must be irritated before the discharge can pass over to the motor cortex The sensations will begin in a part as the movements do in motor attacks and spread to contiguous parts They will be in the nature of a numbness or tingling The focal manifestations will again be contralateral to the lesion

The characteristic type of attack occurring in temporal lobe lesions is the uncinate fit This consists of a bad taste in the mouth the perception of a disagreeable odor and often visual phenomena The odor and taste are not lateralized, but the visual phenomena are in the opposite visual field as one would expect These visual phenomena vary from micropsia or macropsia (images become small or big) to highly systematized hallucinations Sometimes the hallucinations are Lilliputian and the unreal objects that are seen are dwarfed and sometimes they are elaborate panoramas with a succession of figures appearing or events taking place Frequently in attacks arising in the temporal lobe there are sucking or smacking movements of the lips Sometimes also auditory phenomena such as noises occur and occasionally the attacks take the form of dreamy states

these functions have complicated courses and are distributed to both temporal lobes so that a unilateral cortical lesion does not result in a loss of the function. Irritative lesions in the temporal lobe frequently produce a characteristic syndrome which is pathognomonic of the condition. Uncinate fits occur and these are described under the heading of focal epileptic manifestations and there is usually in addition a hemianopsia in the opposite visual field because of involvement of the optic radiations. When these radiations leave the external geniculate body they widen out into a large area, part of which curves forward and laterally into the temporal lobe. If only part of this curving band is destroyed, the visual field defect will be a quadrantic one instead of a full half field blindness.

The parietal lobe situated above the temporal lobe is also a large sensory area concerned with somatic sensibility. It has been stated that the sensory pathways terminate in the thalamus from which new thalamocortical pathways arise. Those concerned with somatic sensibility pass proximally through the posterior part of the internal capsule to reach the cerebral cortex. Most of the fibers are distributed to the post Rolandic convolution but others go to more posterior parts of the parietal lobe and also to the pre Rolandic cortex which as has been stated, is primarily motor. Dusser de Barenne was able to induce sensory changes in animals by local strychninization of both the pre Rolandic and post Rolandic areas. The same segmental arrangement has been described in the post Rolandic convolution as in the pre Rolandic motor area with leg uppermost, arm and trunk in the middle and face and other cranial structures in the lowermost portion, but this is not as definite in its arrangement as in the motor cortex. Evans who carried out careful sensory studies on human beings after ablation of areas of cortex found that astereognosis and impairment of discriminatory sense necessary to appreciate differences in texture, weight, form and consistency occurred after ablations of areas in the region of the supramarginal gyrus. He proposed that primary cortical centers in the anterior parietal region are linked by association neurones with an integrative center at the highest cortical sensory level in the supramarginal gyrus and that in this integrative center transmutation of sensory impulses to psychic activity occurs. This view is somewhat similar to that of Campbell who considered that each perceptual sensory cortical center is surrounded or adjoined by a corresponding psychic sensory level.

In the occipital cortex the visual cortical center borders on the calcarine fissure and is easily distinguished by a thin macroscopic, white line of Baillarger, which runs through the grey matter and because of which the area is called area striata or striate cortex. In this region the visual fibers from the external geniculate body of the same side terminate and within it there is a strict localization of the fibers from the various quadrants of the retina. The final termination of the fibers from the macula has not yet been finally decided. The prevailing opinion is that they are distributed over a wider area and extend farther forward than the remainder of the visual fibers, but there is some evidence to suggest that they may have a bilateral representation in both occipital lobes.

Sensory aphasia consists of a difficulty or inability to understand spoken symbols as such Hearing is not impaired and there is no difficulty in the perception of the word as a sound but it cannot be understood as a proposition It is in this type of aphasia that speech is most grossly disturbed The importance of sense preceptions as a guide to the proper functioning of motor activities is such that in this sensory disturbance motor speech functions are also almost always impaired The sensory defect may be complete or it may be manifest only in complex situations which demand the understanding of propositional symbols

Alexia and agraphia are defects in written speech comparable to sensory and motor aphasia in spoken speech The former consists of a difficulty in understanding written words as symbols and the latter an inability to make use of written words for the expression of propositions The defects vary from time to time as those of spoken speech The writing of words and sentences spontaneously or to dictation or efforts to copy them from models shown may all be impaired Letters are omitted from words or words from sentences or improper ones are used so that the result may bear little or no resemblance to what it should

The same sort of difficulties may be apparent in the use of figures in arithmetical problems in the appreciation and use of musical symbols and in the appreciation and use of objects Shown a match and a matchbox the patient may not be able to name either of them nor recognize the name when it is spoken to him or presented to him in writing but on the other hand he may be able to show perfectly by his actions that he knows the objects and how they are to be used and for what purposes

While these subdivisions have been made it is important to realize that the complex function of speech is not something made up by the addition of certain circumscribed parts It is a function based upon the integrity of certain sensory pathways carrying perceptions into cortical centers of centers of sensory elaboration which will build up these perceptions into conceptions brought into relationship with other conceptions of associational pathways interrelating the many nervous mechanisms involved of memory and general intelligence and of centers having to do with the translation of psychic processes into motor phenomena The result is that there is not a speech center but a function of speech which depends upon the integrating of many nervous mechanisms of different complexities

It is reasonable then that when speech is impaired the impairment should manifest itself in all components of speech functions and this is almost always true It is just as reasonable however that involvement of some of the subcortical connections and pathways concerned with the different functions involved may occasionally impair one modality of speech and leave the others almost intact and this does occur at times Such a selective disorder occurs particularly with occipital lobe lesions which encroach upon or otherwise impair the functioning of the region of the angular gyrus In such cases the speech defect is almost exclusively one of reading and writing and it is only after very careful examination that minimal defects in other speech functions can be found In general it seems that lesions in the anterior part of the

In occipital lobe lesions the focal symptoms are visual and are perceived in the opposite visual field. They may take the form of lights or colored stars, etc. Following these paresthesiae, or instead of them, there is frequently a clouding or a blindness in a quadrantic or hemianopic field.

Aphasia

Disturbances of speech, or aphasia, constitute one of the most difficult problems in the realms of neurology and psychology. Speech, as distinct from articulation, is a function closely linked with other intellectual functions, but it may be impaired in nervous diseases without obvious defect in the remainder of intelligence. It is controlled by one cerebral hemisphere, the left hemisphere in right handed people, and the right hemisphere in left handed people, although there are numerous exceptions to the latter. No adequate explanation has been offered for this dominance of one hemisphere over the other. Since 1861, when Broca described a case of aphasia in a patient with a lesion in the posterior part of the third frontal convolution, an area since then associated with his name, the question as to whether specific cortical centers for speech exist has been a matter for controversy. Without entering into this controversy it may be stated that destructive lesions in the dominant hemisphere in an area extending from the posterior part of the third frontal convolution through the island of Reil, the superior temporal convolution and into the angular gyrus, will produce aphasic manifestations.

These manifestations may be subdivided into the following groups: (1) disturbances in the initiation of spoken speech, motor aphasia; (2) disturbances in the reception of spoken speech, sensory aphasia; (3) disturbances in the initiation of written speech, agraphia; (4) disturbances in the reception of written speech, alexia. Such an arbitrary subdivision is not without danger because the occurrence of each of these groups as an entity is denied by many, and the very terms are anathema to them. On the other hand, it has the advantage of simplicity of description of these conditions as static phenomena.

Motor aphasia may be complete so that the patient cannot speak at all, or it may be partial so that the patient although speechless is not wordless. The latter is the characteristic state and in it the use of words as propositions may be impossible although their use as expletives or in response to emotional stimulus remains. Sometimes the defect is so great that speech becomes an unintelligible jargon and at others it consists merely of a groping for the proper word, a difficulty in finding it and the use of improper terms in its place. Such patients speak slowly and are frequently aware of their inadequacy and their use of wrong words. Perseveration is often noted and the patient having used one term or answer in a certain situation will repeat it in following situations to which it is no longer applicable. A special type of motor aphasia is the so called nominal aphasia in which the defect is present only on attempting to name objects held up to view. It is characteristic of aphasic patients that their performance from day to day and from hour to hour varies greatly and for this reason frequent testing of their reactions in and to certain situations is important.

which arise from these ganglionic cells are the postganglionic fibers or the grey rami communicantes and are not myelinated Some of the grey rami reenter the spinal nerves and carry vasomotor and secretory impulses to the skin and arteries of the extremities others form nerves going to the plexuses in the thoracic and abdominal cavities The afferent sympathetic fibers are not broken up in this way but pass from the organ directly into the spinal cord through the posterior nerve roots in the ganglia of which their cells are located they are myelinated throughout

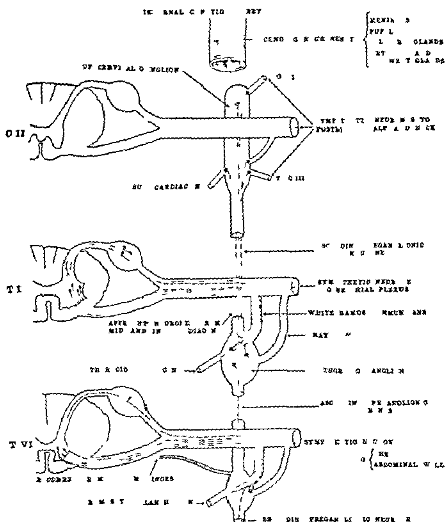


Fig 389—Diagram of the peripheral ... ral n ur nes ... preganglionic motor neurone ... postganglionic motor neurone ... visceral sensory neurone (From White The Autonomic Nervous System The Macmillan Company New York)

The parasympathetic nerves made up of cranial and sacral divisions differ from the sympathetic in that they do not traverse the sympathetic ganglionated chain and that their postganglionic fibers arise from plexuses in the wall of the viscus that they are supplying It has been shown that vaso dilator fibers pass through the posterior spinal nerve roots but their exact nature has not yet been determined

cortex concerned with speech will cause motor speech disturbances, in the posterior part, disturbances in reading and writing, and in the region of the temporal lobe and island of Reil marked disturbances in all types of speech

Apraxia, which is in many ways analogous to motor aphasia, is an inability to perform purposive movements on volition, depending, not upon a defect in the innervation for the several components of the act, but upon inability to combine these to carry out the act Thus a patient with normal power, sensation and coordination may be unable to button his coat, although all the individual movements necessary can be done perfectly In some cases he is no longer able to appreciate the purposive movement that should be carried out and, for example, if given a knife and fork will be entirely unaware of how they should be used These defects seem to arise from impairment of function of cortical areas in the dominant frontal and parietal lobes

The Autonomic Nervous System

The autonomic nervous system should not be considered as something separate from the remainder of the nervous system It has centers, afferent pathways efferent pathways and intercalated pathways like the remainder of the nervous system Its efferent axones pass out in the cranial nerves and the anterior roots of the spinal cord, and its afferent axones enter the brain and cord by way of the cranial nerves and the posterior nerve roots It differs only in that it has different central nuclei and connections, a different mode of peripheral distribution and that it innervates different organs than the systems that have been considered above It is divided into two main divisions which reach the periphery through the peripheral nerves in the following ways the craniosacral or parasympathetic division sends fibers through the third seventh, ninth, and tenth cranial nerves, and the second third and fourth sacral roots the thoracolumbar or sympathetic division leaves the spinal cord through the thoracic nerves and the first and second lumbar roots In the diencephalon in the hypothalamic region, a group of nuclei exist which have been demonstrated to be the head centers for autonomic function It is possible that pathways connect up these nuclei with cortical centers This has not been proved but Fulton and his collaborators have described vascular and intestinal symptoms after ablation of the premotor cortex

The sympathetic gangliated chain lies close to the vertebral column on each side and extends throughout its length At intervals along this chain sympathetic ganglia exist which correspond to the spinal nerves In the neck the ganglia fuse into three the superior cervical the middle cervical which may or may not be present and the inferior cervical which together with the first thoracic forms the stellate ganglion In the thoracolumbar region from which the sympathetic fibers arise each anterior nerve root gives off a white ramus communicans which arose from the intermedio lateral group of cells in the corresponding segment of the cord and which is a preganglionic fiber (Fig 389) These fibers enter the ganglionic chain where some synapse immediately with other groups of cells some ascend or descend the chain to synapse in ganglia at different levels and others pass through the gangliated chain to synapse with cells in the splanchnic plexus The nerve fibers

Table XIII

The Segmental Motor Innervation of the Viscera

Organ	Segments which give off parasympathetic neurones			Segments which give off sympathetic neurones													
				Thoracic												Lumbar	
	Higher cranial segments	Vagus nerve	2nd to 4th sacral nerves	1	2	3	4	5	6	7	8	9	10	11	12	1	2
Eyes	+			+													
Salivary glands					+												
Blood vessels of meninges and brain				+													
Blood vessels of head and neck				?		+	+										
Sweat glands of head				?	+		+										
Blood vessels sweat glands and erector pilae muscles of arms				?	?	?	+		+		+						
Heart					+		+	+									
Lungs		+			+	+		+		+							
Esophagus stomach liver pancreas and small intestine		+							+	+		+	+	+			
Adrenal														+	+		
Kidney		?													+	+	
Bladder			+													+	+
Genitalia																+	
Sigmoid and rectum			+													+	+
Blood vessels sweat glands and erector pilae muscles of legs															+	+	+

From White The Autonomic Nervous System The Macmillan Co

The autonomic nervous system innervates involuntary, smooth muscles and glands This includes the muscles of the iris, the lacrimal glands, salivary glands, sweat glands and secretory glands of the gastrointestinal tract and of other mucous membranes, also the heart and blood vessels and the muscles and sphincters of the hollow viscera, the bronchi, gastrointestinal and genito urinary tracts It keeps the "milieu interieur" (Bernard) of the body constant and regulates the mechanisms concerned in heat production and loss the mobilization of glycogen in the liver, the rate and force of the heartbeat, the peripheral arterial flow, the blood volume and hematopoiesis, the movement and evacuation of the abdominal viscera These regulations, which together have been called "homeostasis" by Cannon, are mediated through the dual action of the sympathetic and parasympathetic divisions The sympathetic system is the catabolic system that is called upon to meet emergencies and protect the body from them It stimulates heat production raises the level of the blood sugar, increases the rate of the heart, diminishes peripheral and so increases central blood flow, and inhibits the activity of the abdominal viscera The parasympathetic is the anabolic or building up system the action of which is antagonistic to that of the sympathetic system These functions may be influenced as a whole or in part

Both the sympathetic and the parasympathetic systems can be influenced by drugs and by hormone secretions The sympathetic system is stimulated by adrenalin and sympathin and depressed by ergotoxine, ergotamine and nicotine The parasympathetic system is stimulated by pilocarpine, choline compounds and by pituitrin given intraventricularly and depressed by atropine and nicotine

In recent years investigations by Dale by Cannon and his coworkers, and by others, have shown that the action of the autonomic nervous system is brought about by means of chemical mediators which are set free when the system is stimulated Thus stimulation of the sympathetic system causes the liberation of sympathin, which, by cross circulation experiments and by its action on denervated organs, has been shown to stimulate those structures ordinarily stimulated by the sympathetic nervous system and to inhibit those ordinarily inhibited Its site of action is somewhere between the nerve ending and the organ itself as it is effective even after the nerve endings have degenerated It is readily diffusible in the blood and so can cause a widespread response after a limited stimulation In the same way a substance is released when the parasympathetic system is stimulated This is a choline compound which is very quickly destroyed and the activity of which is consequently restricted

The following two tables from White* are included to show the segmental innervation both motor and sensory of the autonomic system

Because of its widespread distribution and of its importance to the proper functioning of the internal organs the autonomic nervous system forms an integral part of every other system in the body Recent studies have indicated a close relationship between impairment of sympathetic function and many diseases, and efforts to correct this by surgical means have often been

* The Autonomic Nervous System The Macmillan Company New York 1935

involved Disease in the nervous system may produce multiple or diffuse involvement as in disseminated sclerosis or single focal lesions as in new growths In the latter case the correct anatomical diagnosis depends upon finding the location in which one lesion will involve several cell groups or tracts at the same time so as to produce the physical signs that are manifest In the same way vascular lesions when single must be located in a region that will explain their symptomatology upon a single destructive focus Apart from the general multiple or diffuse diseases and the single focal ones, there are certain diseases which characteristically pick out certain functional units and involve them alone such for example as progressive muscular atrophy which involves the motor cells in the anterior horns of the spinal cord or subacute combined degeneration which involves the pyramidal tracts and posterior columns of the cord

In the sections dealing with disturbances of motility this aspect of the anatomical diagnosis became apparent in the explanation of crossed paralyses These paralyses involving a cranial nerve on one side and the arm and leg on the opposite side could be due to a single lesion in only one location the level of origin of the cranial nerve involved on the same side If it were higher than this the cranial nerve involvement must be contralateral the same as the paralysis of the arm and leg whereas if it were lower the cranial nerve would escape altogether

In the same way in cases of thrombosis of the posterior inferior cerebellar artery because of involvement of the area in the medulla supplied by this artery a group of physical signs occur which must be in relation to a lesion there and not elsewhere These signs vary somewhat depending upon the exact distribution of the artery but the characteristic syndrome consists of (1) hemianalgesia and thermal hemianesthesia alternans the distribution being most often over the face on the side of the lesion and over the body contralaterally this results from involvement of the descending nucleus and tract of the trigeminal nerve and of the spinothalamic tract (2) homolateral laryngo velo palatine palsy from involvement of the nucleus ambiguus (3) Horner s syndrome (constricted pupil narrow palpebral fissure and enophthalmos) from paralysis of fibers to the cervical sympathetic chain on the side of the lesion (4) usually some cerebellar signs on the side of the lesion from involvement of the inferior cerebellar peduncle (Russel and Stavraky)

Lesions in the cerebellopontine angle especially eighth nerve tumors characteristically cause tinnitus and later nerve deafness from direct involvement of the auditory nerve cerebellar signs on the same side of the body from direct involvement or pressure on the cerebellum and its pathways and pyramidal tract signs on the opposite side of the body from pressure on the pyramidal tract before its crossing in the medulla Of course all these signs may or may not be present depending upon whether the fiber tracts named are involved or not and in addition adjacent cranial nerves may be included in the lesion

Single focal lesions in the cord can in the same way and usually do involve several structures Compression of the cord by an extramedullary tumor usually produces as its first symptom girdle pains or root pains from

followed by excellent results This branch of surgery has been exploited particularly in the treatment of peripheral vascular disease and also in retinitis pigmentosa angina pectoris hypertension, Hirschsprung s disease peptic ulcer and in intractable pain arising from the viscera

TABLE XIV

SENSORY INNERVATION OF THE VISCERA

ORGAN	SUPERFICIAL AREAS TO WHICH PAIN IS REFERRED	SEGMENTS AT WHICH VISCERAL AFFERENT NEURONES ENTER SPINAL CORD	AUTHORITY
Meninges	Side of scalp and face	T T_2	Dandy (1931)
Heart	Precordium and inner arm	T T_8	Mackenzie (1923), White, Garrey and Atkins (1933)
Lung	No evidence of pain till parietal pleura and intercostal nerve are involved	---	White (unpublished data)
Esophagus	Substernal distress	T T_8	von Gaza (1924)
Liver and Gallbladder	Right upper quadrant distress with pain referred to right scapular region	T T_4	von Gaza (1924)
Stomach	Epigastric region	T_7 T_8	von Gaza (1924)
Small Intestine	Umbilical region	T_8 T_9	von Gaza (1924)
Colon	Suprapubic region	T I_2	Lawen (1923) von Gaza (1924)
Kidney	Loin and groin	T_2 L	von Gaza (1924) White and Garrey (unpublished data)
Ureter	Loin and groin	L L	Lawen (1923) Wharton (1932)
Bladder	Suprapubic region	T_1 L	Pieri (1926) Learmonth (1931)
Uterus	Suprapubic region and lower back	T L_2	Cleland (1933)

While it has been demonstrated that the sympathetic rami from the bladder and ureter reach the ganglionated chains as low as their fourth lumbar segments this does not imply that sensory impulses run into the cord as low as this Indeed Head and Riddock s (1893) observations on the areas of referred pain from the bladder point to the first or second lumbar segments as the lower limit (From White The Autonomic Nervous System The Macmillan Co)

Summary

The foregoing sections have been devoted to an explanation of the symptomatology following diseases of the chief nuclei and fiber pathways of the nervous system By the proper interpretation of the symptomatology one is able to determine in large measure the structures that are involved and where in their course they are involved and consequently to locate anatomically the disease process This is the clinical application of the known facts in regard to neuroanatomy and neurophysiology From the standpoint of description and explanation it has been necessary to deal with the individual systems separately but disease ordinarily does not restrict its ravages to one system and allow the others to remain free The problem of anatomical diagnosis becomes therefore a plural one It is more often than not a question of which several pathways are involved and where in their courses they are

the preservation of afferent impulses from the muscles so that it is a true reflex In addition certain postural arrangements can be produced by impulses arising from muscles in the neck and from impulses arising in the labyrinth These impulses are induced by altering the position of the head relative to the body after the semicircular canals have been destroyed (tonic neck reflexes) or by turning of the head in space without altering its relative position to the body, or after the sensory nerves from the neck have been destroyed (tonic labyrinthine reflexes) Apart from the extensor rigidity and the reflexes described above, the ability to reflexly right the body when its position has been altered is also lost The righting reflexes are lost because of separation of midbrain nuclei from the lower centers and the reflex postures are induced through the mediation of brain stem nuclei separated from the inhibiting and modifying influence normally exerted by higher centers

THE PATHOLOGICAL DIAGNOSIS OF NERVOUS DISEASES

Because of the distinctive cells, the nerve cells and interstitial cells which occur in the nervous system pathological conditions produce changes which are different and more complex than those elsewhere in the body



Fig 390 —Central chromatolysis (retrograde degeneration) Ganglion cell from the nucleus ambiguus in case of amyotrophic lateral sclerosis ... Nissl bodies ... at periphery of swollen cell ... Nucleus ... (From Weil A Text book of Neuropathology Lea and Febiger Philadelphia 1933)

It has been stated that the nerve cells vary in size and shape and that they have an efferent process called the axone which is usually covered with myelin In addition other processes called dendrites are present but these are expansions of the cell body itself and have the same structure Fixed and stained nerve cells have a nucleus and nucleolus chromophilic granules called Nissl granules and neurofibrils The Nissl granules are present in the cell body and dendrites but not in the axone or the region about its origin from the cell body Neurofibrils are seen to traverse the cell body and all its processes When an axone, covered with myelin leaves the central nervous system to pass into the peripheral nerves it acquires another covering the neurilemma or sheath of Schwann which has nuclei along its course At regular intervals along this sheathed nerve there are constrictions called nodes of Ranvier and each area of the sheath of Schwann between these nodes is nucleated

irritation of the posterior nerve roots These pains are present, either on one side or both, in the segmental distribution of the nerve roots involved The paths within the cord which appear to be most vulnerable to the effects of such compression are the pyramidal tracts, and signs of their involvement may be present as the only evidence of the lesion for some time A hemisection of the cord, or a lesion involving one half of the cord, will cause a Brown Sequard paralysis In the segmental distribution of the lesion and on the same side there will be (1) a loss of all forms of sensation, from involvement of the posterior nerve roots (2) a lower motor neurone type of paralysis from involvement of the anterior horn cells and their axones passing into the anterior roots The level symptoms from involvement of the tracts in the white matter, and these are the characteristic manifestations of this syndrome, will be (1) a homolateral, spastic, upper motor neurone type of paralysis below the lesion from involvement of the pyramidal tract, (2) a loss of position and vibration sensibility on the same side of the body at all levels below the lesion from involvement of the posterior columns and (3) a loss of pain and temperature sensibility on the opposite side of the body at all levels below the lesion, from involvement of the spinothalamic tract

Complete sudden transection of the spinal cord results in a temporary condition of "spinal shock" in which all reflexes are absent tonicity is lost and sphincter control is abolished As all the fiber pathways have been sectioned there is of course an abolition of all voluntary motor power and of all sensation below the lesion After an interval which may be long in man this condition of shock begins to wear off and certain reflex activities mediated by centers below the transection, begin to return Tonus begins to return to the limbs and stimulation of the legs or feet or frequently at any point below the transection, will cause a triple flexion mass reflex of the legs This is a defense reaction and may occur on both sides after unilateral stimulation Its chief feature is withdrawal of the limb by means of flexion at the hip, knee and ankle When the plantar response first returns it is a flexor response *which gradually is replaced by plantar extension The mass flexion reflex* may be induced by the lightest of stimulation even the weight of a sheet, and may be so forcible and marked as to be accompanied by evacuation of the bowels and bladder and by profuse perspiration below the level of the lesion Spastic paraplegia (upper motor neurone paralysis of both legs) due to an incomplete lesion of the cord may leave the legs in a position of extension or of flexion The former is the more common and the latter position is attributed to a constant stream of stimuli entering the cord and causing a constant triple flexion reflex of the legs which remain in a position *of flexion* Thus paraplegia in flexion is believed to be due to involvement of the vestibulo spinal pathways in addition to the pyramidal tracts while *paraplegia in* extension is supposed to occur when the vestibulospinal tracts escape

Section of the brain stem at a point distal to the red nuclei and proximal to the vestibular nuclei produces a condition of decerebrate rigidity This is manifested by a marked increase in tonus of extensor muscles the muscles which maintain an erect or standing position and act against gravity Because of this, reflex standing occurs and the maintenance of this depends *upon*

the preservation of afferent impulses from the muscles, so that it is a true reflex In addition certain postural arrangements can be produced by impulses arising from muscles in the neck and from impulses arising in the labyrinth These impulses are induced by altering the position of the head relative to the body after the semicircular canals have been destroyed (tonic neck reflexes) or by turning of the head in space without altering its relative position to the body, or after the sensory nerves from the neck have been destroyed (tonic labyrinthine reflexes) Apart from the extensor rigidity and the reflexes described above the ability to reflexly right the body when its position has been altered is also lost The righting reflexes are lost because of separation of midbrain nuclei from the lower centers and the reflex postures are induced through the mediation of brain stem nuclei separated from the inhibiting and modifying influence normally exerted by higher centers

THE PATHOLOGICAL DIAGNOSIS OF NERVOUS DISEASES

Because of the distinctive cells the nerve cells and interstitial cells which occur in the nervous system, pathological conditions produce changes which are different and more complex than those elsewhere in the body



Fig 390 —Central chromatolysis (retrograde degeneration) Ganglion cell from the nucleus ambiguus in case of amyotrophic lateral sclerosis Cresyl violet. Nissl bodies well preserved at periphery of swollen cell but lacking in center Nucleus situated eccentrically and mildly swollen (From Weil A Textbook of Neuropathology Lea and Febiger Philadelphia 1933)

It has been stated that the nerve cells vary in size and shape and that they have an efferent process called the axone which is usually covered with myelin In addition other processes called dendrites are present but these are expansions of the cell body itself and have the same structure Fixed and stained nerve cells have a nucleus and nucleolus chromophilic granules called Nissl granules and neurofibrils The Nissl granules are present in the cell body and dendrites but not in the axone or the region about its origin from the cell body Neurofibrils are seen to traverse the cell body and all its processes When an axone covered with myelin leaves the central nervous system to pass into the peripheral nerves it acquires another covering the neurilemma or sheath of Schwann which has nuclei along its course At regular intervals along this sheathed nerve there are constrictions called nodes of Ranvier and each area of the sheath of Schwann between these nodes is nucleated

Pathological processes will produce changes in all these structures Interruption of the axone or disease affecting the cell body will produce alterations in the cell Ordinarily this consists of swelling of the cell body which becomes spherical The nucleus, which is normally located in the center of the cell, becomes displaced to one side The Nissl granules undergo chromatolysis and gradually disappear either from the center of the cell or its periphery (Fig 390) If the damage is not too great the changes reverse and the cell returns to normal As cell disintegration continues, it is hastened by phago

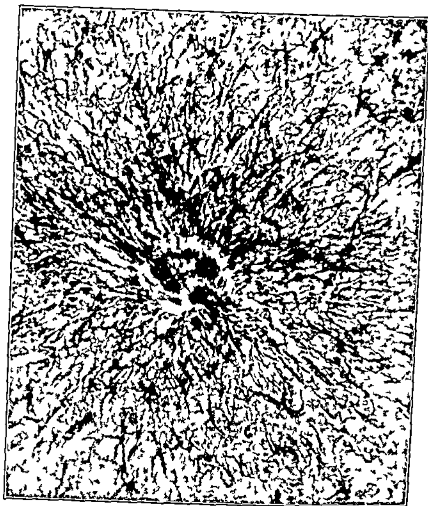


Fig 391 —Stab wound of fifteen days standing in brain of rabbit showing concentric arrangement of astrocytes expanding toward the connective tissue core Cajal's gold chloride astrocyte stain (From [illegible] Principles of the Pathology of Neurosurgery Nelson's Loose Leaf Surgery Thomas Nelson and Sons 19[illegible])

cytic cells which also remove the debris, and this process is called neuronophagia The end result is either atrophy, which leaves only a shadow cell behind, or complete disappearance of the cell Separation of the axone from its cell, either by damage of the former or disease of the latter, will result in Wallerian degeneration in the part of the axone separated and also a retrograde degeneration from the point of separation up to the next node of Ranvier The myelin sheath undergoes changes and the myelin becomes broken up into droplets which are removed by phagocytic cells The axone

also disintegrates and is removed In the central nervous system where *the axones have no sheath of Schwann this process is an irreversible one* and regeneration cannot occur In the peripheral nerves on the other hand, the degenerative changes in myelin and axone are coincident with regenerative efforts in the sheath of Schwann, the nuclei of which increase As long as continuity remains in this sheath, or if it be reestablished regeneration *is possible Consequently peripheral nerves can regenerate while central* pathways cannot This type of Wallerian degeneration has been of great value in the study of neuroanatomy Experimental lesions will cause the degeneration and while this is progressing distribution of the nerve fibers and tracts can be followed by special staining methods, especially the Marchi method

Astrocytes are fibrous or nonfibrous (protoplasmic) The former are present chiefly in white matter the latter in grey matter They are large *stellate cells which have numerous processes a large pale nucleus and no* nucleolus Characteristic of them is the fact that they have one or more perivascular or pial feet attached to blood vessels or pia Acute degenerative changes in the astrocytes consist of swelling of the cell body and its expansions, the latter of which gradually break off piece by piece to leave behind an ameboid cell body *The most acute change according to Cone is a frag*mentation of the expansions of the cell with little or no swelling In areas of softening or *inflammation or degeneration the astrocytes multiply and form a* wall around the lesion Later the cells shrink and leave a dense network of glia fibers containing few cell bodies (Fig 91) The astrocytes take no part in phagocytosis

Oligodendroglia, so called because they have few expansions have little *cytoplasm and no perivascular or pial feet* They occur in long parallel rows between myelinated fibers and as perineuronal satellites As suggested in the *introduction to this chapter they may be concerned with the formation and* preservation of myelin Penfield and Cone were the first to fully describe acute swelling of oligodendroglia a pathological change which is found in acute intoxications certain mental diseases (Elvidge and Reed) and in patients who have died in coma This change is apparently a reversible one in which the cell becomes swollen pale and vacuolated (Fig 92) The processes break up into granules and even the cell membrane may disintegrate and leave a naked nucleus behind Apparently this change is a very *sensitive one as it* may be present without any changes in other cells On the other hand acute *changes in astrocytes are practically always accompanied by alterations in* oligodendroglia

Microglia cells are of mesodermal origin and develop chiefly immediately after birth They are small cells with expansions containing spines at right angles and have an elongated triangular or curved nucleus They have no fibrils and no foot plate They are more numerous in the grey than in the white matter and are sometimes closely applied to nerve cells as satellites though this is more characteristic of oligodendroglia than of microglia Microglia cells become ameboid and phagocytic in disease and carry products of disintegration of myelin and of broken up astrocytic expansions to blood vessels It is presumed that they discharge these waste materials into the

blood vessels on the walls of which the fully laden cells congregate These phagocytic cells are called compound granular corpuscles or scavenger cells, and are formed through swelling of the microglia which become rounded and withdraw their processes (Fig 593) They also form elongated rod cells such as are found in the brains of paretics

Just as the anatomical diagnosis of nervous diseases depends primarily on a proper interpretation of the physical signs, so the clinical pathological diagnosis is made largely from the history of the illness and the results of special examinations These diseases etiologically may be subdivided into the following groups



Fig [illegible] —Extreme swelling of three oligodendroglia cells which are perineuronal satellite Small granules and vacuoles representing broken up expansions are present Silver carbonate stain for oligodendroglia (From Cone Acute Pathological Changes in Neuroglia and in Microglia Arch Neurol and Psychiat July 1928)

1 Diseases due to prenatal influences or to familial constitutional defects In these the history frequently though by no means always dates from the time of birth This is particularly true in the prenatal diseases which are not familial as spina bifida with meningeal protrusions In the familial diseases symptoms may be noticed from early infancy as in amaurotic family idiocy from childhood or youth as in Friedreich s ataxia or not until mature adult life, as in Huntington s chorea Some of these prenatal conditions are developmental defects such as incomplete or imperfect development of certain parts of the nervous system some are diseases transmitted to the offspring

such as congenital syphilis, while still others are truly hereditary and transmitted in the germ plasm

2 *Traumatic diseases may be acquired at the time of birth or any other time during life* The history of symptoms immediately following a trauma in an individual previously healthy is of course of great value in pointing to their cause It must be borne in mind, however that trauma may be sustained at the onset of a nontraumatic illness such as during an epileptic attack or at the onset of a sudden vascular lesion in the brain In these cases subsequent symptoms may be due to the trauma or to the coexistent disease The use of x rays and of lumbar puncture are of great aid in determining the traumatic nature of neurological signs Apart from the symptoms which supervene at the time of the accident there may be immediately or as long delayed as several years posttraumatic sequelae such as epilepsy, whose relationship to the trauma may be hard to determine

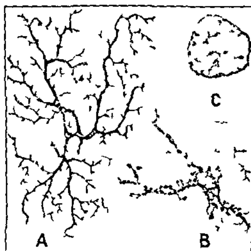


Fig [illegible] —Transitional stages from the microglia cell A to the compound granular corpuscle C (From Penfield Principles of the Pathology of Neurosurgery Nelson Loose-leaf Surgery Thomas Nelson and Sons New York 19[illegible])

3 Acute inflammatory diseases may or may not be due to a demonstrable infection or infestation with parasites In these cases the history is usually a short one and it is frequently possible to point to infection elsewhere in the body such as tuberculosis or acute middle ear suppuration which may have spread to the nervous system Lumbar puncture is of great value in the diagnosis of these conditions when they are in communication with the subarachnoid space in which the cerebrospinal fluid circulates Usually on physical examination other evidence of the inflammatory process is apparent such as fever The chronic inflammatory diseases notably syphilis also cause changes in the cerebrospinal fluid

4 Intoxications may occur from endogenous poisons as in delirium or from exogenous poisons In the latter cases signs may follow within a short time of the assimilation of the poison as in alcoholism or after a very long interval as in lead poisoning It is often possible in these cases to obtain

a history of exposure to the poison or to find signs elsewhere in the body, in the blood, or in the excreta, which point to the cause of the disease

5 New growths are usually single focal lesions They may be metastatic from elsewhere in the body or, more frequently, primary in the nervous system The history in these cases is usually a long one extending over a period of months but sometimes symptoms may come on suddenly even though the tumor has been growing silently for a long time The history of progression over a period of months, the signs of a single focal lesion, the evidence of increased intracranial pressure and findings on x ray examination all help to establish the diagnosis If the tumor is in the spinal cord, or compressing the spinal cord, the Queckenstedt test and the use of lipiodol, both of which are discussed later, may be of aid The characteristic symptoms which occur with increased intracranial pressure are headache, vomiting and papilledema or choked optic discs and are described on page 1101 The cause of increased intracranial pressure is usually a growing neoplasm which adds to the intracranial contents Other causes also exist such as hydrocephalus, which may be due to any lesion which blocks the exit of cerebrospinal fluid from the ventricles or interferes with its absorption in the dural sinuses

6 There is a large group of chronic degenerative diseases which affect the nervous system and the etiology of which is unknown Usually these are slowly progressive over a period of years and usually also they are multiple or diffuse Because of their predilection to involve only certain structures as in amyotrophic lateral sclerosis, or the history of their course, as in disseminated sclerosis, they ordinarily fall into groups of definite disease entities For this reason and also because of their long continued course, their diagnosis is not usually difficult

The pathological changes which occur in the various nervous diseases are described under the heading of the specific disease

The Cerebrospinal Fluid

The cerebrospinal fluid is formed by vascular tufts, the choroid plexus, which project into the ventricles and circulates throughout the ventricular system and in the subarachnoid space of the brain and cord It escapes from the ventricles through the foramen of Magendie and the foramina of Luschka situated in the roof of the fourth ventricle The subarachnoid space is not equally deep throughout, as it widens out at the base of the brain around the medulla oblongata, and in other locations, into large cisterns The fluid is absorbed almost entirely through the arachnoidal villi which are projections of arachnoid into the venous sinuses in the folds of the dura In addition it is probable that some of it is absorbed by lymphatics, which it reaches through the funnel like prolongations of arachnoid at the beginning of the cranial and spinal nerves

The formation of this fluid is partly in the nature of a selective filtration and partly a secretion It differs in composition from blood plasma but contains no new substance that is not in the blood Because of the water cushion which it forms about the central nervous system it protects the brain and cord from ordinary jars and concussions In addition it allows the brain

to vary in volume even though it is enclosed within a rigid bony box In crease in volume of the brain forces cerebrospinal fluid into the spinal sub arachnoid space and diminution in volume of the brain allows more fluid to collect in the ventricles and cranial subarachnoid space This mechanical function of the cerebrospinal fluid is not its only one as it is also concerned in the metabolic processes going on in the nervous system The volume of fluid is about 120 c c, and this may be replaced four or five times in twenty four hours

Cerebrospinal fluid may be collected for examination from the subarach noid space below the termination of the spinal cord (lumbar puncture) from the cisterna magna at the base of the brain (cisternal puncture) or from the ventricles (ventricular puncture) Lumbar puncture is carried out by in serting a needle in the midline of the back through an interspace between two of the lower lumbar vertebrae and into the subarachnoid space within the vertebral canal Ordinarily the interspace chosen is the third which is on a level with a line joining the uppermost portion of the two iliac crests The puncture can be done with the patient seated or lying on his side If pressure determinations are of importance in the specific case and they usu ally are the patient should be recumbent Cisternal puncture is made with the patient lying on his side with his head flexed by inserting a needle in the midline of the back of the neck between the lowest point of the occiput and the spine of the atlas As the needle is pushed in it is directed upward until it hits the base of the occiput It is then withdrawn partly and redi rected to a point a little lower than the first and in this new direction it will puncture the dura below the base of the skull As these punctures are being done it is well to withdraw the stylet from the needle at intervals to see whether the subarachnoid space has been reached and whether cerebro spinal fluid can be obtained Ordinarily as the dura is penetrated there is an unmistakable sensation of a give to indicate it In doing a cistern puncture it is not wise to penetrate deeper than 5 5 or 6 cm in the ordinary person and the needle should be marked so that this point will be known Ventricular puncture is made through trephine openings in the skull and with a large blunt needle marked off in centimeters which is inserted into the ventricles through the brain substance It is a surgical procedure which ordinarily should not be carried out unless one is in a position to deal with whatever type of lesion may exist

While ventricular puncture has its limitations in ordinary surroundings lumbar and cisternal punctures have their contraindications They should be carried out with caution if a brain tumor is suspected and ordinarily should not be done at all if there is papilledema indicating increased intra cranial pressure or the suspicion of a tumor in the posterior fossa The reason is that if pressure is released below by removal of fluid and if a lesion in the posterior fossa interferes with the escape of fluid from the intracranial cavity the medulla and cerebellum are likely to be pushed down into the foramen magnum and become compressed and edematous and death may ensue Such pressure cones or cerebral herniations with distinct grooves in them from pressure of the edges of the foramen magnum can be seen on

postmortem examination. Following lumbar puncture patients may complain of headache and even vomiting and a stiff neck. Ordinarily this can be prevented by keeping the patient in bed for twenty-four hours after the puncture. While it is not certain, the cause is probably a continuing leak of cerebrospinal fluid through the hole made in the dura. Forcing fluids, the use of pitressin, as an antidiuretic, and the administration of hypotonic saline solution intravenously, may all be used to overcome the symptoms but the most important thing is to maintain a recumbent position. These symptoms may last as long as five or seven days, although ordinarily they pass off much more quickly.

Normally the cerebrospinal fluid is under a pressure of 80 to 170 mm. with the patient lying on his side and the occiput and lumbar puncture needle in the same horizontal plane. This pressure can be determined easily by connecting an Ayer manometer to the lumbar puncture needle by means of a three-way stopcock. The manometer is a hollow glass tube graduated

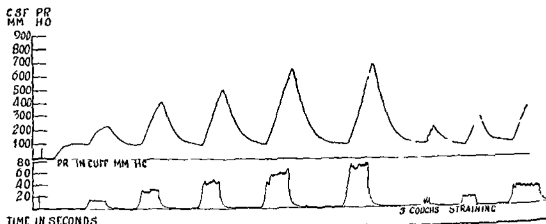


Fig. 394.—A normal tracing of changes in cerebrospinal fluid pressure after compression of the jugular vein. Pressure of spinal fluid in the lumbar subarachnoid space is shown in the top tracing and pressure applied by means of a sphygmomanometer cuff about the neck is shown in the lower tracing. The time is recorded in seconds at the bottom. Application of pressure to the jugular vein results in a rapid and free rise in spinal fluid pressure and release of pressure on the jugular veins causes a rapid free return to original spinal fluid pressure. The greater the pressure applied to the neck the greater the rise in cerebrospinal fluid pressure. Coughing and straining also raise intrathecal pressure. (Courtesy of Drs. W. T. Grant and W. W. Cone.)

in millimeters and when the spinal fluid, which has flowed into the tube, reaches a constant level the pressure can be read off in terms of millimeters of spinal fluid. The fluid level, however, is not at rest because oscillations are transmitted to it coincident with each heartbeat and respiration. This pressure is increased frequently in diseases of the nervous system and this is discussed further in a consideration of the individual diseases.

It is a well-known law of physics that pressure applied to a fluid medium is transmitted equally in all directions through it. This applies to the cerebrospinal fluid circulation and forms the basis of the Queckenstedt test which is used to determine whether or not there is a block in that circulation. Compression of the jugular veins causes blood to dam back within the skull and this raises intracranial pressure. The increase in pressure is transmitted throughout the cerebrospinal fluid and can be measured in the lumbar subarachnoid

space by means of a lumbar puncture needle and manometer Normally compression of each internal jugular vein separately, or both together, causes *a rapid rise in spinal fluid pressure* and, *when the compression is released* the spinal fluid pressure quickly returns to normal The maximum change should occur within 10 to 20 seconds of the application or release of pressure Compression of the jugular veins on the two sides separately need not result in equal increases in spinal fluid pressure but bilateral compression causes a greater increase than unilateral compression In addition to compression of the veins other procedures will increase cerebrospinal fluid pressure Coughing and abdominal straining will do so by increasing the intrathoracic and intraabdominal pressures and impeding venous drainage from the vertebral canal

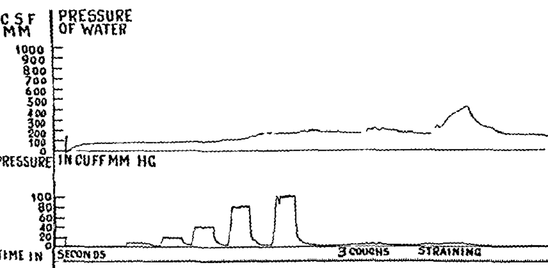


Fig 39 —Tr c ng a in F g 394 but [illegible] complete block (Courtesy of Dr W T Grant and W V Cone)

Grant and Cone have recently modified the Queckenstedt test in an effort to make it more graphic and exact and to make several determinations at different times comparable to one another They apply pressure about the neck by means of a sphygmomanometer cuff and they record on a kymograph the pressure within the cuff and the pressure of spinal fluid in the lumbar region together with a time tracing Two of their records are shown here Fig 394 is a normal tracing Successively greater cuff pressures applied about the neck cause successively greater rises in spinal fluid pressure The response is rapid and the recovery is rapid Coughing and straining also cause coincident increases in pressure Since pressure is transmitted equally throughout the fluid medium the same observations normally can be made on cistern puncture and on lumbar puncture If the two are carried out at the same time equal and practically simultaneous changes should be found in each

If a complete block occurs in the cerebrospinal fluid system the changes in pressure will not be transmitted beyond the block This is shown well in Fig 39[illegible] in which inflation of the cuff is not followed by a rise in cerebrospinal

fluid pressure If a partial block occurs, the changes in pressure will be less pronounced and less rapid than normal and the return to normal, after the release of jugular compression, will not be complete The reason for this last observation is that the increased intracranial pressure may be sufficient to force some fluid past the block, but the pressure within the sac distal to the block is not sufficient to force the fluid back again

Not only will this test show the presence of a block, but it can also be used to show the location of the block If compression of the internal jugular vein on one side is followed by a normal response while on the opposite side there is no response, the block is apparently not in the cerebrospinal fluid circulation but in the venous circulation itself This occurs in thrombosis of the lateral sinus in which compression of the internal jugular vein, on the same side, causes no increase in the venous block which already exists and so no change in intracranial pressure With a block in the vertebral canal such as frequently occurs with cord tumors, a puncture of the cisterna magna will show normal pressure reactions while a lumbar puncture will show evidence of block If the block is high up, in the cervical region, increases in pressure induced by coughing and straining will both be transmitted to the lumbar puncture needle If it is lower, the changes on coughing will not be demonstrable while those on straining will remain, though they may be reduced With a lesion in the lower thoracic or lumbar region both will be abolished It is sometimes possible, in cases of cauda equina lesions, to insert needles both above and below the lesion and the same comparative studies can be carried out in the two

Normal spinal fluid is clear and colorless and contains less than 9 white blood cells per cubic millimeter It has a total protein content that varies from 5 to 35 or 40 mg per cent, depending on its source, and which usually averages about 25 mg per cent The sugar content varies from 50 to 85 mg per cent and the chlorides, as sodium chloride, 700 to 750 mg per cent All these characteristics undergo changes in disease and these are recorded in the symptomatology of the individual diseases

X ray Examinations

By means of x ray examinations a great deal of information can be obtained which forms an important part of the study of many neurological cases The skull and vertebral column like other bony structures, impede the passage of the rays and so can be photographed clearly Their different parts such as the sella turcica the mastoid air cells the accessory nasal sinuses the suture lines the intervertebral discs etc can all be well differentiated In addition, by special posturing various structures such as the optic foramen and the internal auditory meatus can be brought into view and deviations from the normal may be seen The different structures of the brain and cord on the contrary can ordinarily not be seen unless special measures are taken to visualize them

The skull may show deviations from the normal shape and size, its sutures may be prematurely closed or their closure may be delayed because of increase in intracranial pressure Fusion of the bones of the two sides may be incom

plete and cranium bifidum or spina bifida may be apparent By a study of the adult skull and a comparison of the growth of its various parts and of the structures of the face, it may be possible to determine the state of activity which the endocrine glands concerned in growth have exercised during different age periods Changes in the continuity of the bones and in their relationship to one another follow fractures or dislocations or a combination of the two The normal contour and density of the bones of the skull and vertebral column may be altered by disease within themselves or disease involving them from without Erosions occur from tumors within the skull and also from the pressure of meningeal tumors against the inner table of the



Fig 396 —Marked pressure or convolutional atrophy of the skull from increased intracranial pressure Note that the pattern of this atrophy is an imprint of that of the brain surface

skull These erosions may be single or multiple When intracranial pressure is increased generally over a long period of time the pressure of the brain against the skull may gradually cause an atrophy of the latter This atrophy will be present where the convolutions have pressed against the skull but not opposite the sulci where no pressure has been exerted The resulting appearance of the atrophy of the bone will be that of an impression of the surface of the brain (Fig 396) Such an appearance though of lesser degree than that illustrated may be seen normally in the skulls of children without any increase in intracranial pressure In the same way tumors within the vertebral canal may cause some erosion of the bodies of the vertebrae or erosion of the pedicles and widening of the interpedicular spaces

Erosion of the sella turcica by pituitary tumors is well known, but such erosion may also occur with suprasellar tumors at a distance In the same way auditory nerve tumors may erode the internal auditory meatus and meningeal tumors, the optic foramen It is important that all parts of the skull be examined minutely for erosions, proliferations, calcifications, and increased vascularity Proliferative changes may occur side by side with other changes, such as erosion and deposition of calcium It may be due to disease of the bones, as in Paget's disease, or secondary involvement of the bone as in meningeal fibroblastoma In the latter the normal vascular markings are frequently increased in the location of the tumor



Fig 397 —The calcified pineal gland can be seen and behind it and very slightly above are the shadows of the chorioid plexus of each side

Ordinarily the different parts of the brain and spinal cord cannot be differentiated in an x ray film Normal calcifications sometimes occur which may however give a great deal of information about the intracranial contents In adult life the pineal gland is often calcified and this can be seen both in anteroposterior and lateral views (Fig 397) Deviation from its normal position may occur in tumors of the brain Occasionally calcification may occur, presumably without pathological significance in the chorioid plexus this is also shown in Fig 397 Areas of calcification in the falx and in the petroclinoid ligament just behind the sella turcica also occur without obvious disability These are calcifications which are regarded as normal but calcification may occur in connection with pathological lesions, such as old

abscesses and some tumors and hemorrhages In addition, the intracranial portion of the internal carotid artery may occasionally show calcification on x ray examination

In 1918 Dandy introduced a method of x ray examination which has been of inestimable value since As stated above, the intracranial contents cannot *be differentiated from one another Brain substance and the cerebrospinal* fluid within the subarachnoid space and the ventricles cast no distinctive shadows, as they impede the passage of x rays to the same extent. Dandy

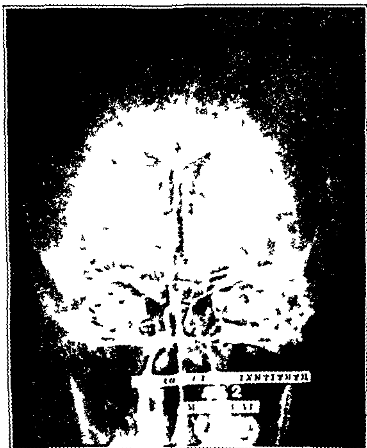


Fig 398.—[illegible] Note the butterfly like configuration of the lat[illegible] *below them of the third ventricle and* the streaky filling [illegible] space

found that if the cerebrospinal fluid is replaced by air, the air containing spaces will then be differentiated on an x ray film from the surrounding structures The exchange can be made by means of a needle inserted into the ventricular system through a trephine opening (ventriculography) or by means of a needle inserted into the lumbar subarachnoid space (encephalography) Ventriculography has the same restrictions as ventricular puncture it is a surgical procedure which should be carried out only if facilities exist to immediately deal with whatever type of lesion is found Encephalography has the same contraindications as lumbar puncture, it should not be

Erosion of the sella turcica by pituitary tumors is well known, but such erosion may also occur with suprasellar tumors at a distance. In the same way auditory nerve tumors may erode the internal auditory meatus and meningeal tumors, the optic foramen. It is important that all parts of the skull be examined minutely for erosions, proliferations, calcifications, and increased vascularity. Proliferative changes may occur side by side with other changes, such as erosion and deposition of calcium. It may be due to disease of the bones, as in Paget's disease, or secondary involvement of the bone as in meningeal fibroblastoma. In the latter the normal vascular markings are frequently increased in the location of the tumor.

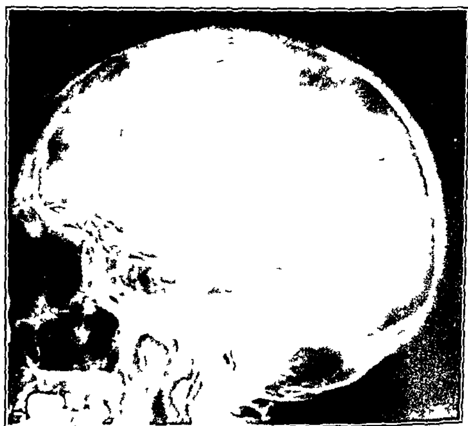


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Ordinarily the different parts of the brain and spinal cord cannot be differentiated in an x ray film. Normal calcifications sometimes occur which may, however, give a great deal of information about the intracranial contents. In adult life the pineal gland is often calcified and this can be seen both in anteroposterior and lateral views (Fig. 397). Deviation from its normal position may occur in tumors of the brain. Occasionally calcification may occur, presumably without pathological significance, in the chorioid plexus; this is also shown in Fig. 397. Areas of calcification in the falx and in the petroclinoid ligament just behind the sella turcica, also occur without obvious disability. These are calcifications which are regarded as normal but calcification may occur in connection with pathological lesions, such as old

Normally the ventricular system lies in the midline (Figs 398 and 399) Distortion filling defects or displacements of it are pathological conditions which will show up in the encephalogram The abnormality may exist throughout the ventricles or it may be limited to one portion

Tumors of the brain displace the system to the opposite side by pushing it away They frequently, also collapse the homolateral ventricle, or a portion of it and dilate the contralateral ventricle Encroachment may be made on any part of the lateral ventricles third ventricle or fourth ventricle If the tumor is in the posterior fossa and interferes with drainage of cerebrospinal fluid it will dilate the entire ventricular system proximal to it In such

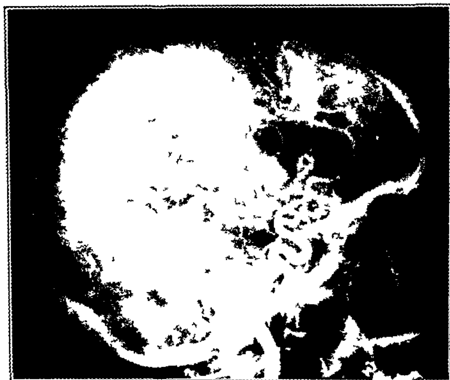


Fig 400 —Outline of the vascular tree during the injection of thorotrast. Note that the anterior and middle cerebral arteries lead to a circumscribed area of increased vascularity This was in the region of a cerebral cicatrix

a case it may not be possible to fill the ventricles from below but only by means of direct introduction of air into them through trephine openings Contracting lesions instead of pushing the brain away exert a traction upon it and distortion of the ventricles may again occur In such a case however displacement will be toward the side of the lesion and not away from it It is frequently found that the part of the ventricle nearest the lesion is pulled out of position On the surface of the brain opposite this pull air may collect in such a quantity as to indicate an area of atrophy or a cystlike collection in the subarachnoid space

By the injection of thorotrast a thorium salt into the internal carotid artery the vascular tree of the brain can be outlined In order that proper

done when a posterior fossa tumor is suspected or when there is papilledema suggesting the presence of tumor of the brain

Encephalography can be done with the patient in an erect sitting position or lying on his side It is possible by posturing the patient to direct most of the air to the site desired Ordinarily when this procedure is carried out as a diagnostic test, it is desired to fill both the ventricles and subarachnoid space and it is done with the patient erect At other times the aim is to direct the air chiefly to the subarachnoid space and in this case the patient is made to lie on his side with that part of the head uppermost where filling should be most complete This particular posturing is used chiefly in cases of subarachnoid



Fig 399 — A normal encephalogram Lateral view of the ventricles and subarachnoid space

adhesions and posttraumatic headache The exchange of cerebrospinal fluid and air or oxygen is carried out fractionally and slowly and an effort is made to keep the cerebrospinal fluid pressure as nearly constant as possible In this way it is possible to withdraw as much as 100 to 120 c c of spinal fluid and inject the same or a little greater amount of air

After the injection x rays are taken in anteroposterior, posteroanterior and right and left lateral positions By gently manipulating the head and posturing it, air can be directed into the various parts of the ventricular system for photography Stereoscopic plates are taken so that three dimensional studies can be made In addition by placing the brow or the occiput uppermost air can be directed to the anterior or the posterior portions of the system

x rays It can be introduced into the cisterna magna and allowed to descend in the subarachnoid space by gravity It is also sometimes given into the lumbar subarachnoid space and the patient is then tilted with the head downward so that gravity will carry the substance higher into the vertebral canal In the presence of an obstructing lesion such as a tumor or adhesions the substance will be held up by the obstruction and the level of this arrest can be determined by x ray examination Fig 401 was taken after the injection of lipiodol, both into the cisterna magna and into the lumbar subarachnoid space and the x ray film shows how well outlined are the upper and lower borders of the obstructing lesion Recently a compound named pantopaque has been introduced which is supposed to be less toxic has less local irritating effects and can be more easily removed in whole or in part If the responses to the Queckenstedt test are normal it is unnecessary to inject these substances as there is apparently no obstruction to the flow of cerebrospinal fluid If however the responses to jugular compression indicate that there is a block and if clinically the level of this block cannot be determined then they can be used to advantage

DISEASES OF THE NERVOUS SYSTEM

Diseases Due to Prenatal Influences

Dysplasia

Defects in growth may occur at any time during the development of the nervous system If this happens early or if the structural defect is a severe one it may be incompatible with life or result in the formation of a monster The defect may take the form of absence of parts, even of the cerebral hemispheres (anencephaly) or spinal cord (amyelia) The failure of development may be more restricted to a single structure or unit such as the corpus callosum certain cranial nerve nuclei or motor or sensory pathways A part even though present may fail to attain its proper growth The brain may be small (microcephaly) and enclosed in a small skull The deficient growth may be limited to one half or to the gyri of the cerebral hemispheres (microgyria) It has been found that with microgyria in one cerebral hemisphere there is usually also imperfect growth in other regions of the nervous system such as the opposite cerebellar hemisphere Failure of development of parts based upon their position in the phylogenetic scale has been described and Brouwer has reported atrophy of the neocerebellum and of the neo olives with preservation of the phylogenetically older parts of both

The reverse condition is shown in macrogyria in which the brain is considerably larger than normal Another abnormally excessive type of growth is reduplication of the lower part of the spinal cord in which an apparently normal cord lies side by side with a smaller replica Heterotopia is a condition in which certain structures or cellular groups become displaced from their normal positions during development such as cellular groups normally present in grey matter being displaced into white matter

With these various defects in growth the symptomatology may vary greatly In some cases a live birth is impossible In others monsters are born who live but for a short time On the other hand it is surprising what de

pictures be obtained, a special routine is necessary X ray exposures must be made at the most frequently possible intervals during the administration of the substance Thorium, like other metals, impedes the passage of x rays and so the vessels containing this substance show up sharply on the film Fig 400 shows the result of such a method By this means abnormalities in the



Fig 401 —Upper and lower borders of a tumor of the spinal cord outlined by means of lipiodol

blood vessels themselves such as aneurysms and abnormal vascularization in the region of other lesions become apparent This procedure should be carried out with caution, as thorotrast is an irritant in perivascular tissues and is also a radioactive substance (see pages 750 and 1114)

For some years lipiodol (iodine in vegetable oil) was used to locate blocks in the spinal subarachnoid space This substance is also opaque to

velopmental defects may occur with little or no symptomatology, much less in fact than if a *comparable* condition had been produced by disease Mentality is frequently retarded in these conditions and epileptic attacks are common symptoms The diagnosis depends upon the history of the case and also upon the appearance of the patient if this is at all characteristic These conditions being developmental defects are not amenable to treatment, but if the resulting disability is slight, it is possible, by training and education, to bring about improvement in the individual's capacity

Cranium Bifidum and Spina Bifida

Definition—Cranium bifidum and spina bifida are defects resulting from imperfect closure of the bony structures of the skull and vertebral column in the midline It occurs most frequently in the vertebral column, as spina bifida

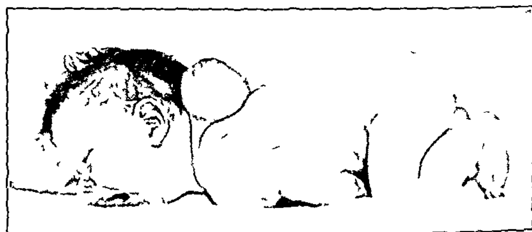


Fig 402—Spina bifida with meningocele in the cervical region

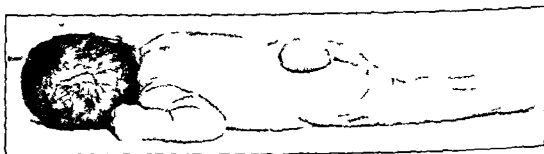


Fig 403—Spina bifida with meningocele in the lumbosacral region

and especially in the cervical (Fig 402) and lumbosacral (Fig 403) regions as these are the last to unite Cranium bifidum also usually occurs posteriorly and rarely in the frontal region The defects may be apparent or they may be so slight as to escape notice, in which case they are called occult In the vertebral column the imperfect fusion is almost always posteriorly, but very rarely it occurs anteriorly as well Through the defect in the bone meninges may protrude and form a sac covered by thin tissue paper like skin over the region of the defect This condition is known as a meningocele Within the meningocele traction may be made on nervous structures which become ad

Etiology—The etiology is unknown It is possibly due to a disturbance in lipoid metabolism It has been described in association with Niemann Pick disease (page 578) and the same type of cellular changes has been found in the two conditions

Symptoms—The ordinary form of this disease is the infantile in which symptoms first appear about the age of three or four months There are progressive apathy and a gradually increasing muscular weakness and flaccidity first noticed in an inability to hold up the head Vision becomes impaired and optic atrophy and blindness follow The cherry red spot which *is characteristic of this disease is seen in the macula fovea Weakness spreads* throughout the body emaciation follows the reflexes become increased, and spasms and convulsions may occur During the course of the illness the muscles may be spastic for a time The mental enfeeblement is progressive to the point of idiocy Death usually occurs within two years

A *late infantile type (Bielschowsky Jansky type) also exists in which* symptoms first appear about the age of three or four years and in which the patient may live about four years There is also a juvenile type (Spielmeyer Vogt type) beginning between the ages of seven to twelve years running a longer course not associated with macular changes and occurring in Gentiles

Pathology—This disease is characterized by widespread cellular changes The nerve cells become swollen and pear shaped the nucleus is pushed to the side and the cytoplasm becomes a homogeneous lipoid substance which bulges the cell membrane The neurofibrils occupy the periphery of the cell body and around the nucleus there may be remains of Nissl substance

Prognosis—The disease progresses until death occurs Its duration may vary from one to eight or ten years The earlier the onset the shorter the duration

Treatment—There is no known treatment

Pelizaeus Merzbacher Disease

Synonym—Aplasia axialis extracorticalis congenita

Definition—A rare congenital and familial disease characterized by diffuse demyelinization in the brain

Etiology—This disease may be a chronic type of diffuse sclerosis and it is possible that it is an acquired and not a congenital disease

Symptoms—There may be an acute or subacute onset beginning at the age of one to five years and then followed by a chronic course Ordinarily there are ataxia and spasticity of the legs nystagmus slowness of speech and mental retardation There may be optic atrophy and abnormal movements either coarse tremors or choreiform movements

Pathological Anatomy—There is diffuse demyelinization of the white matter of the brain without inflammatory reaction but with extensive glial proliferation

Tuberose Sclerosis

Synonyms—Epiloia tuberous sclerosis

Definition—A disease manifested by adenoma sebaceum intellectual retardation and epilepsy

present and epilepsy occurs frequently in these individuals In marked cases of mental deficiency the defect becomes apparent early in the life of the child, while in borderline cases it may pass practically unnoticed and the individual may be self supporting throughout his life By means of standardized tests, such as the Binet Simon tests, the intelligence quotient, the ratio of mental age to chronological age can be determined Sometimes stigmata, such as dispro portionate features, may be apparent Occasionally psychotic symptoms occur on a basis of mental deficiency and sometimes also stereotyped movements appear Because of the low intellectual level and judgment, the patient may require watching to be kept out of trouble

Treatment —The higher grade mental defectives may frequently be trained in some simple occupation which will make them self supporting Lower grades are not amenable to such training and may require institutional care because of their dependence, or behavior disorders, or because of epilepsy which may be associated

Mongolian Idiocy

Synonym —Mongolism

Definition —Idiocy in association with mongoloid features (eyes slant downward and inward, the nose is broad and flat, the tongue thick and fis sured) a small skull and sometimes other congenital anomalies

Etiology —This is unknown The condition has been attributed to the age of the parents and the number of children previously born to them, but these are doubtful etiological factors Mongolian idiocy has been described in identical twins which indicates a determining factor in the germ plasm The presence of mongolism in only one of dissimilar twins supports this Mongolian idiots are frequently born to people of superior intelligence

Symptoms —The striking feature of this condition is the mongolian facies and this, in conjunction with the idiocy and the small skull flattened both in front and behind is usually sufficient to establish the diagnosis The chief differentiation that must be made is from cretinism (p 927) The presence of congenital cardiac lesions, a protuberant abdomen and large flat hands and feet aid in the diagnosis The intellectual defect is a marked one

Pathological Anatomy —The brain is small and there is an aplasia of cells cell layers and sometimes entire gyri

Treatment —There is no treatment for this condition Usually the indi vidual dies in infancy or soon after although occasionally one has lived to adult life

Amaurotic Family Idiocy

Synonym —Tay Sachs disease

Definition —A disease occurring in infancy and characterized by progres sive mental enfeeblement, muscular weakness, optic atrophy and blindness and the occurrence of a cherry red spot in the macula of the retina

Incidence —This is a familial disease which is almost exclusively confined to Jews and which usually affects more than one child in the family

defect may be more marked in the Rolandic area where the nerve cells are fewer in number, the cell layers poorly developed and there is a hyperplasia of neuroglia cells and fibers

Prognosis—The disability may remain stationary or show a slight, gradual improvement Some cases progress In itself this condition does not threaten life but like so many other diseases with this degree of incapacity the individual is less resistant to intercurrent disease

Treatment—The treatment consists of education and training and orthopedic measures to overcome or prevent deformities In those cases which tend to improve and in which there is no great mental retardation, much can be *done by proper exercises Massage and passive movements are also of value*

Infantile Cerebral Hemiplegia

Definition—A hemiplegia present from birth and due to a lesion within the brain

Etiology—Birth trauma or disease affecting the brain before or immediately after birth

Symptoms—This condition, although not a developmental disease, is discussed here because sometimes it is bilateral and may resemble infantile cerebral diplegia In bilateral infantile hemiplegia however the arms are more involved than the legs signs of other lesions are frequent and mentality is more often impaired than in infantile cerebral diplegia The symptoms and signs are those of an upper motor neurone lesion, together with whatever pathological signs may be present due to other lesions Athetoid movements frequently occur in this condition due to involvement of the basal ganglion In infantile hemiplegias it is not uncommon to find the abdominal reflex preserved The growth of the involved member or side may be retarded so that it remains throughout life smaller than its opposite Convulsions later in life are a frequent occurrence

Pathological Anatomy—Since this condition can depend on so many causes the pathology varies Birth hemorrhages inflammatory diseases, lacerations of the brain all occur Following them there is often focal atrophy of the area of brain involved with atrophy of nerve cell elements and overgrowth of astrocytes

Treatment—In these cases also training psychotherapy physiotherapy and orthopedic measures are the only methods of treatment but a great deal can be accomplished through assessing and developing their assets rather than by trying only to remedy their liabilities The treatment of convulsions is discussed in the section on Epilepsy (page 1155)

Double Athetosis

Synonym—État marbre of Oppenheim and C Vogt

Definition—Athetosis on both sides without pyramidal tract signs occurring as a congenital disease

Symptoms—Increased tone and athetotic movements on the two sides The movements are more marked in the upper extremities but may occur in

Etiology —It is sometimes familial and is due to a congenital abnormality

Symptoms —The epileptic attacks begin early and may be major or minor focal or nonfocal About the age of 4 or 5 years the adenoma sebaceum appears on the face This spreads over the bridge of the nose and cheeks in *the shape of a butterfly* The spots are raised, pink or red, and some are discrete and some confluent The mental retardation is quite marked As tumors may appear in other organs of the body, such as the heart or kidney, they may sometimes cause symptoms The tumors in the brain do not usually cause focal symptoms but may if they grow sufficiently large Other congenital anomalies, such as hare lip or heart disease, may be present Blood relations of the patient may show other skin abnormalities

Pathological Anatomy —In the cerebral cortex there are numerous hard, white tumors, varying in size from that of a pea to that of a walnut These are made up of altered nerve cells and glia cells The cells in the cortex of the brain show changes and the gyri may show enlargement in places Tumors or cystic degeneration may be present in other regions of the brain as well especially about the ventricles Tumors appear elsewhere in the body, in the heart, kidneys, thyroid, skin, retina etc

Treatment —There is no specific treatment for the condition and the only treatment is symptomatic

Infantile Cerebral Diplegia

Synonyms —Little's disease, congenital spastic paralysis

Definition —A diplegia (paralysis of both sides) which is more marked in or confined to, the legs and is present from birth

Etiology —It is always difficult to decide whether an infantile cerebral diplegia is due to a developmental defect or a birth trauma to the brain It is probable that either may be the etiological factor or perhaps a combination of the two Other etiological factors may also be responsible

Symptoms —The symptoms are those of bilateral pyramidal tract involvement and are more marked in the legs and may be confined to them The disability may escape notice at the time of birth and become recognized because of the slowness of development and the difficulty in learning to walk The weakness is symmetrical and may be marked or slight with only reflex changes When very marked the feet are in a position of *equino varus* and the increased adductor tone crosses one leg over the other so that the patient walks with a "scissors gait" In addition to the spastic paralysis there may be cerebellar signs abnormal movements such as chorea or athetosis (Fig 408) cranial nerve weakness and deformities of the spine In many cases the mental level is normal and the children are bright and alert In others there is some degree of mental retardation Convulsions may also be present This condition seems to be associated with prematurity in many cases It has been found in siblings

Pathological Anatomy —There may be gross developmental defects in the brain (microcephaly) or in the convolutions (microgyria) or both The

defect may be more marked in the Rolandic area where the nerve cells are fewer in number, the cell layers poorly developed and there is a hyperplasia of neuroglia cells and fibers

Prognosis—The disability may remain stationary or show a slight gradual improvement Some cases progress In itself this condition does not threaten life but like so many other diseases with this degree of incapacity the individual is less resistant to intercurrent disease

Treatment—The treatment consists of education and training and orthopedic measures to overcome or prevent deformities In those cases which tend to improve, and in which there is no great mental retardation, much can be done by proper exercises Massage and passive movements are also of value

Infantile Cerebral Hemiplegia

Definition—A hemiplegia present from birth and due to a lesion within the brain

Etiology—Birth trauma or disease affecting the brain before or immediately after birth

Symptoms—This condition, although not a developmental disease is discussed here because sometimes it is bilateral and may resemble infantile cerebral diplegia In bilateral infantile hemiplegia, however the arms are more involved than the legs signs of other lesions are frequent and mentality is more often impaired than in infantile cerebral diplegia The symptoms and signs are those of an upper motor neurone lesion, together with whatever pathological signs may be present due to other lesions Athetoid movements frequently occur in this condition due to involvement of the basal ganglion In infantile hemiplegias it is not uncommon to find the abdominal reflex preserved The growth of the involved member or side may be retarded so that it remains throughout life smaller than its opposite Convulsions later in life are a frequent occurrence

Pathological Anatomy—Since this condition can depend on so many causes the pathology varies Birth hemorrhages inflammatory diseases lacerations of the brain all occur Following them there is often focal atrophy of the area of brain involved with atrophy of nerve cell elements and overgrowth of astrocytes

Treatment—In these cases also training psychotherapy physiotherapy and orthopedic measures are the only methods of treatment but a great deal can be accomplished through assessing and developing their assets rather than by trying only to remedy their liabilities The treatment of convulsions is discussed in the section on Epilepsy (page 1155)

Double Athetosis

Synonym—État marbre of Oppenheim and C Vogt

Definition—Athetosis on both sides without pyramidal tract signs occurring as a congenital disease

Symptoms—Increased tone and athetotic movements on the two sides The movements are more marked in the upper extremities but may occur in

Etiology—It is sometimes familial and is due to a congenital abnormality

Symptoms—The epileptic attacks begin early and may be major or minor focal or nonfocal About the age of 4 or 5 years the adenoma sebaceum appears on the face This spreads over the bridge of the nose and cheeks in the shape of a butterfly The spots are raised, pink or red, and some are discrete and some confluent The mental retardation is quite marked As *tumors may appear in other organs of the body*, such as the heart or kidney, they may sometimes cause symptoms The tumors in the brain do not usually cause focal symptoms but may if they grow sufficiently large Other congenital anomalies such as hare lip or heart disease, may be present Blood relations of the patient may show other skin abnormalities

Pathological Anatomy—In the cerebral cortex there are numerous hard, white tumors, varying in size from that of a pea to that of a walnut These are made up of altered nerve cells and glia cells The cells in the cortex of the brain show changes and the gyri may show enlargement in places Tumors or cystic degeneration may be present in other regions of the brain as well especially about the ventricles Tumors appear elsewhere in the body, in the heart kidneys thyroid, skin, retina, etc

Treatment—There is no specific treatment for the condition and the only treatment is symptomatic

Infantile Cerebral Diplegia

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Etiology—It is always difficult to decide whether an infantile cerebral diplegia is due to a developmental defect or a birth trauma to the brain It is probable that either may be the etiological factor or perhaps a combination of the two Other etiological factors may also be responsible

Symptoms—The symptoms are those of bilateral pyramidal tract involvement and are more marked in the legs and may be confined to them The disability may escape notice at the time of birth and become recognized because of the slowness of development and the difficulty in learning to walk The weakness is symmetrical and may be marked or slight with only reflex changes When very marked the feet are in a position of equino varus and the increased adductor tone crosses one leg over the other so that the patient walks with a scissors gait In addition to the spastic paralysis, there may be cerebellar signs, abnormal movements such as chorea or athetosis (Fig 408) cranial nerve weakness and deformities of the spine In many cases the mental level is normal and the children are bright and alert In others there is some degree of mental retardation Convulsions may also be present This condition seems to be associated with prematurity in many cases It has been found in siblings

Pathological Anatomy—There may be gross developmental defects in the brain (microcephaly) or in the convolutions (microgyria), or both The

the pyramidal tracts and the spinocerebellar tracts, with a secondary gliosis

Prognosis—The disease may remain stationary but is usually very slowly progressive so that it may result in complete incapacity

Treatment—There is no specific treatment

Hereditary Cerebellar Ataxia

Synonym—Marie s ataxia

Definition—Another type of hereditary ataxia in which *the manifestations* are more truly cerebellar and in which the skeletal deformities are not present It is sometimes very difficult to differentiate this from Friedreich s ataxia, as well as from other conditions described below, and they probably represent the same type of abiotrophy with more restricted or widespread involvement in the different cases

Symptoms—These closely resemble the symptoms of Friedreich s ataxia as far as ataxia nystagmus and speech disturbances are concerned The onset is later than in Friedreich s disease and there is no scoliosis nor deformity of the foot The tendon jerks are increased and there is a bilateral Babinski sign In addition there may be ocular manifestations such as optic atrophy or paralysis of external ocular muscles Special forms have been described by Sanger Brown and by Dejerine and Thomas The Sanger Brown type comes on later and the pathological changes are almost confined to the spinocerebellar tracts The posterior columns may be involved but the corticospinal tracts usually escape Ataxia speech disturbance spontaneous movements ocular palsies and optic atrophy occur The Dejerine Thomas type has a widespread involvement of the cerebellum and pons and begins in middle life

Pathological Anatomy—As in Friedreich's ataxia there is an atrophy of nervous elements and a replacement with glial scar There is degeneration of the spinocerebellar tracts the cerebellum and the pyramidal tracts

Hereditary Spastic Paraplegia

Definition—A rare hereditary and familial disease manifested by a slow progressive paralysis of the legs beginning at the age of five or seven and *increasing for many years The paralysis is of an upper motor neurone type* and shows the characteristic signs Contracture may occur and the disease may spread to the upper limbs and cranial nerves

Etiology—Unknown regarded as an abiotrophy

Pathological Anatomy—There is agenesis of the spinal cord and degeneration of the pyramidal tracts In late cases the posterior columns and direct spinocerebellar tracts may also be involved

Family Periodic Paralysis

Definition *—A rare familial* disease *manifested* by recurring spells of flaccid paralysis

Etiology—*Unknown* This disease may skip a generation or may involve several members of the same family

Symptoms—*In an otherwise healthy individual* attacks of paralysis occur usually during sleep which involve different muscle groups and more than

the toes as well Athetosis is a frequent accompaniment of diseases affecting the pyramidal tract before, during, or immediately after birth, but in addition it may occur without pyramidal tract involvement

Pathological Anatomy—The lenticular nuclei have the appearance of marble and for that reason the condition has been called etat marbre There are areas of atrophied ganglion cells and a resulting sclerosis in the caudate nucleus and the putamen of the lenticular nucleus the globus pallidus is less involved

Treatment—There is no specific treatment for this condition Symptomatic treatment with stramonium and hyoscine will probably not help greatly The entire question of the treatment of extrapyramidal motor diseases has been stimulated by the study of surgical section of extrapyramidal pathways in the anteromedian part of the cord as introduced by Tracy Putnam

Friedreich s Ataxia

Synonym—Hereditary ataxia

Definition—This is one of a group of hereditary ataxias which merge into one another and which frequently cannot be positively differentiated from one another There is degeneration of the posterior columns of the spinal cord the pyramidal tracts and the spinocerebellar pathways

Etiology—The disease is hereditary and frequently occurs in siblings Its ultimate cause is unknown, but it has been grouped among the abiotrophies or diseases due to inability of certain parts of the nervous system to develop fully to functional maturity

Symptoms—The disease first manifests itself about the time of puberty Ataxia or incoordination appears first in the lower extremities and gradually extends to involve the whole body This ataxia may be manifested on movement or at rest Walking is interfered with the patient walks on a broad base and sways as he does so Dysmetria and dyssynergia are present in movements of the hands and arms Movements are clumsily carried out Spontaneous irregular movements of the head and shoulders and extended limbs occur Tonicity and reflexes will depend upon the relative involvement of the posterior columns and pyramidal tracts There may be hypotonia or spasticity and the tendon reflexes may be absent or increased Frequently the knee jerks are increased and the ankle jerks absent The plantar response is extension Nystagmus and speech disturbances are characteristic The speech becomes monotonous and slurred or scanning or staccato and sometimes explosive Skeletal deformities occur such as scoliosis and a typical deformity of the foot which is shortened has a high exaggerated longitudinal arch and hyperextended toes so that the big toe may assume the position which is ordinarily shown in a Babinski response Sensory changes are not common although impairment of position and muscle sense may occur The disease may be fully manifested in one member of a family and only some of its symptoms such as the deformity of the foot may appear in others

Pathological Anatomy—The spinal cord is small and the cerebellum also may be smaller than normal There is degeneration in the posterior columns

Progressive Lenticular Degeneration

Synonyms—Wilson s disease hepato lenticular degeneration

Definition—A familial disease manifested by rigidity, involuntary movements degeneration of the lenticular nuclei and cirrhosis of the liver

Etiology—Unknown considered perhaps to be toxic in origin

Symptoms—The onset is during the second decade of life The course may be acute, subacute or chronic There is a rigidity which may lead to contractures Abnormal movements such as tremor, choreic or athetotic movements are present There are no pyramidal tract signs and no true paralysis sensory loss or reflex changes Because of the spasticity and movements voluntary motion is impaired, and this causes difficulty in swallowing and talking as well as in the use of the limbs There is often an emotional disturbance, and late in the illness there may be some deterioration In a few cases a ring of greenish brown pigmentation has been found around the cornea There is marked cirrhosis of the liver

Pathological Anatomy—There is degeneration in the lenticular and caudate nuclei This may spread from these nuclei into surrounding structures and cavitation may occur The cirrhosis of the liver is a mixed type

Prognosis—In the acute cases death may ensue within a few months Other cases last for several years before death occurs

Treatment—There is no known treatment

Pseudosclerosis

Synonym.—Westphal s disease

Definition—Although this disease was first regarded as a separate entity it is now considered a form of progressive lenticular degeneration

Symptoms—This disease begins in young people with tremor of one limb which gradually spreads to involve the entire body There is muscular rigidity movements are slow and the face expressionless and masklike Personality changes and dementia occur These conditions exhibit the signs of extrapyramidal motor system disease with increase in tonicity, the presence of abnormal involuntary movements, the slowness and stiffness of voluntary movement and the masklike face

Pathological Anatomy—The pathology is like that of Wilson s disease, with degeneration of the lenticular nucleus and glial proliferation The changes in pseudosclerosis are not as gross as those in Wilson's disease and in addition the cerebral cortex may be involved

Prognosis—Death usually occurs within a few years

Treatment—There is no treatment

Amyotonia Congenita

Synonyms—Myatonia congenita, Oppenheim s disease

Definition—A condition of extreme muscular hypotonia without true paralysis

Etiology—This is considered to be a congenital disease of the lower motor neurones and the muscles

one extremity at a time The paralysis may spread to involve all the limbs and sometimes the trunk musculature The signs are those of a flaccid, lower motor neurone paralysis with loss of tendon jerks and abolition of galvanic and faradic excitability The cranial nerves are rarely involved There are sometimes electrocardiographic changes, bradycardia and cardiac dilatation during an attack It begins in early life lasts many years and the individual attacks last from one hour to several days

Pathological Anatomy—This is unknown and cannot be demonstrated even on post mortem examination

Prognosis—The condition lasts for many years Occasionally death may occur in an attack Biemond and Polak Daniels have recently described this condition passing over into a permanent muscular weakness

Treatment—Recently it has been shown that these attacks are associated with marked decrease in the serum potassium and that the administration of potassium at the onset of an attack, either by mouth or intravenously, may cause the paralysis to disappear or to improve within a short time The daily administration of potassium chloride, 4 to 6 grams may prevent the attacks from occurring

Huntington s Chorea

Synonym—Hereditary chorea

Definition—An hereditary disease manifested by chorea, beginning in middle age and progressive dementia

Etiology—This is a true hereditary disease which is more common in America than in Europe It has been possible to trace large numbers of these cases back to the original carriers Davenport in studying the heredity of nearly 1000 cases found that practically all could be traced back to some half dozen individuals including three brothers who came to America in the seventeenth century Both sexes transmit the disease, but those who remain free of it will not transmit it Owing to its late onset an individual may marry and only later develop the symptoms

Symptoms—The onset is usually about the age of thirty to forty five years The progress is slow and insidious and it may begin with the involuntary movements or the mental change The movements may begin in the face or upper limbs but gradually involve the entire body They are rapid, jerky, twisting irregular choreic movements which cause grimacing dysarthria and difficulty in walking and in using the arms The mental change is a gradual deterioration sometimes with depression delusions and irritability Suicide is not uncommon among these patients

Pathological Anatomy—There is atrophy of the brain especially of the frontal lobes and the corpus striatum (caudate and lenticular nuclei) The ganglion cells in these regions are atrophied and reduced in number There is a glial proliferation in these atrophied areas

Prognosis—The prognosis is bad as the disease is chronic and progressive and usually terminates fatally in ten to fifteen years

Treatment—The only treatment of the disease is institutional care Sedatives may help

Myotonia Congenita

Synonym—Thomsen's disease Although the name is somewhat the same, this condition is not related to myatonia congenita Myotonia is an increased tonus of muscles, myatonia or amyotonia is a lack of tone or an atony of muscles

Definition—An hereditary disease manifested by difficulty in starting contraction and relaxation of muscles and consequently a slowness in changing the posture of muscles and in initiating movements

Etiology—The disease is hereditary and has been described in seven generations of Thomsen's own family

Symptoms—The symptoms first become apparent in childhood although in some cases they are not noticed until adult life When an attempt is made to carry out a voluntary movement it is difficult to overcome the tonus of muscles and so to start the movement Thus if the patient starts to fall, he cannot bring muscles into action to right himself sufficiently quickly, in walking the first few steps are taken slowly and with great difficulty then the muscles loosen up and the patient can walk well on being told to grasp something *the patient cannot do so until an interval has elapsed* In the same way relaxation is difficult If the patient has something in his grasp and is told to let go he cannot do so immediately but an appreciable interval passes before he can relax his grip Response to tapping the muscle and electrical stimulation of it show the same phenomena the response is delayed and slow and prolonged There is no wasting of muscles in fact they may be enlarged and reflexes and sensation are normal The disease varies in severity and in location It may be generalized or restricted, *especially to the lower limbs* Sometimes eye movements show the same defect and the patient is unable to conjugately deviate the eyes quickly The symptoms are worse during emotional stress and *exposure to cold* and there is one type in which the symptoms are present only on exposure to cold

Pathological Anatomy—In this condition there are no objective signs in the nervous system The muscle fibers are large there are many nuclei and the cross striations are poorly defined

Prognosis—*The disease is incurable but sometimes shows temporary arrest.*

Treatment—It has been shown that quinine hydrochloride by mouth in doses of 2½ to 15 grains two or three times a day will consistently eliminate myotonia as a disturbing symptom* In this connection the section on myasthenia gravis (page 114[illegible]) should be read

Myotonia Atrophica

Synonym—Myotonic dystrophy

Definition—*A rare disease manifested by myotonia atrophy of special* muscle groups and a family history of cataracts The disease is familial and hereditary but some cases occur without such a history

Symptoms—Myotonia is most marked in the hands and exhibits the characteristics described under Myotonia Congenita The atrophy picks out cer

* Kennedy and Wolf J A M A 110 No 3 198, 1938

Symptoms—These may be apparent from birth or escape notice until it is found that the child cannot hold up its head and is incapable of maintaining other postures. There is an extreme hypotonia which prevents the child from sitting or standing or keeping its limbs or head in an unsupported position. The various parts can be moved voluntarily if they are supported. Because of the hypotonia the patient can be placed in unusual positions, the thighs can be flexed right up against the body wall so that the feet can be crossed behind the head. When the child is raised from the floor or bed by support in the axillae it tends to fall through these points of support, so that the shoulders are raised high and the trunk and head seem to be slipping through. Although the muscles are small, there is no localized atrophy, and there are no fibrillary twitchings in the muscles. Smooth muscle is not involved and the intercostal muscles and diaphragm escape. The tendon jerks are diminished or absent, faradic excitability is diminished or lost, and galvanic excitability is retained.

Pathological Anatomy—The muscles show the presence of some abnormally small fibers and some hypertrophied ones. In addition some apparently normal fibers remain. There is an increase in the number of nuclei in the muscles and an increase also in connective tissue. Changes in the anterior horn cells are discussed under the heading of Werdnig Hoffman Disease.

Prognosis—This disease tends toward gradual improvement, until the patient becomes able to walk and live actively.

Treatment—There is no specific treatment. Physiotherapy and training help while improvement is taking place.

Werdnig Hoffman Disease

Definition—A disease clinically like amyotonia congenita but beginning later and having a familial history.

Symptoms—*By many authors this is considered* to be a type of amyotonia congenita. It occurs in siblings and there is also frequently a history of the same disease in previous generations or in collaterals. Before the onset of symptoms the child is apparently normal. At the age of two or three years the disease first manifests itself. The same type of weakness occurs but it is associated with atrophy and begins in the proximal parts of the limbs and then extends downward. There are no fibrillary twitchings and the same changes occur in the reflexes and electrical responses as in amyotonia congenita.

Pathological Anatomy—Grinker has described the following changes in the anterior horns of the cord in these two diseases. In amyotonia congenita he found a paucity of anterior horn cells and the presence of abnormal cell types without signs of degeneration. In the Werdnig Hoffman type of muscular atrophy there were signs of degeneration in the anterior horns with chromatrolysis and vacuolization of nerve cells, neuronophagia, glial proliferation and signs of degeneration in the anterior nerve roots.

Prognosis—There is gradual progression and death follows within a few years.

Treatment—There is none known.

Types—(1) The pseudohypertrophic type of Duchenne In this type pseudohypertrophy of the calf muscles is a prominent feature and sometimes pseudohypertrophy occurs in the deltoid and other shoulder muscles as well The chief difficulty is in the legs the gait is waddling, the children fall easily and they have difficulty in climbing stairs They have the characteristic way of rising from a lying to a standing position described above The large calves feel hard and unnatural, and late in the disease the hypertrophied muscles may also atrophy This type is most common in childhood and in several members of a family and there is often no history of the disability in preceding generations (2) Juvenile form of progressive muscular dystrophy or Erb's type In this type the shoulder girdle is first involved and then the condition spreads to the trunk, arms and thighs The face forearm and legs are involved only very late (3) Facio scapulo humeral or Landouzy Dejerine type In this the muscles of the face shoulder girdles and upper arms are affected and there is no hypertrophy There may be difficulty in closing the eyes and wrinkling the forehead The lips taper outward and the lower lip curves downward When smiling the corners of the mouth do not turn upward and the smile is transverse' The infraclavicular region is flat and hollowed across the chest and the arms cannot be raised because of involvement of the deltoid muscles Later muscles of the trunk may be affected and lumbar lordosis and an awkward gait appear (4) Mixed types The types above described run true to form in a great many families and individual cases Sometimes, however the distribution of the myopathy may be different and mixed types occur

Pathological Anatomy—The pathological changes are in the muscles and not in the nervous system Nevertheless these conditions are usually described in sections on neurology because of their similarity to neurological diseases and because a gradual transition occurs between the neurological and nonneurological types of muscular atrophy and weakness Differentiation between the two is sometimes difficult In the primary myopathies the hypertrophied muscles are made up of large swollen fibers with an increased number of nuclei a loss of striations and some increase in connective tissue and deposition of fat In the atrophied muscles and the hypertrophied muscles when they begin to atrophy the fibers are small the nuclei diminished and the connective tissue increased These two types of changes may go on side by side Evidence of disturbance of muscle metabolism is found in an increased excretion of creatin in the urine

Prognosis—The prognosis is bad as the atrophy and weakness progress

Treatment—Treatment has been investigated along three lines (1) on the basis that endocrine dysfunction occurs (2) the use of adrenalin and pilocarpine on the assumption that there is a functional disorder of the autonomic nervous system (3) the use of glycine or other amino acids, in an effort to overcome the disturbance in muscle metabolism Of these the last seems to be the only method that offers promise Glycine in daily doses of 5 to 20 gm at first increases the creatin output and then diminishes it and brings it to a normal level Clinical improvement has been described at the same time

tain muscle groups, the orbicularis oculi and oris, the sternomastoids, the muscles of the forearm and of the thighs The atrophy may be extreme, especially in the sternomastoid muscles Changes occur in the teeth and skin and hair There is loss of tendon jerks, and sensory changes may occur There may be excessive lacrimation and salivation Cataracts occur characteristically in this disease, and often the evidence of heredity may be limited to the presence of cataracts, occurring at a young age, in the forebears of the patient The disease begins usually about the age of twenty or thirty years but may begin at a younger age, especially in families in which it is well established

Pathological Anatomy—There is a degeneration of muscle fibers and a proliferation of connective tissue Reduction in the number of anterior horn cells has also been described

Treatment—As for myotonia congenita

Hereditary Progressive Muscular Dystrophies

Synonyms—Primary myopathies, muscular dystrophy, myopathic atrophy

Definition—A chronic, progressive disease manifested by atrophy and weakness of certain muscle groups, sometimes associated with pseudohypertrophy, and frequently occurring as an hereditary or congenital disease

Etiology—Other than heredity there is no known cause The disease is one of the muscles and apparently not of the nervous system

Symptoms—The myopathies usually become apparent in childhood, sometimes a little later In one family several members may show the condition and sometimes also it is to be found in preceding generations The characteristic finding is atrophy in certain groups of muscles, and the myopathies have been subdivided depending upon the distribution of the atrophy The atrophy is associated with weakness and both are progressive Sometimes certain groups of muscles show hypertrophy or pseudohypertrophy They become larger than normal but yet are not normal and are weaker than normal Later in the disease these pseudohypertrophic muscles also atrophy Males are more often affected than females and in one family the children of one sex may be involved and not those of the other With the weakness there is clumsiness and these patients find great difficulty in using the involved members The standing posture is characterized by a protuberant "pot belly" with markedly increased lumbar lordosis and with winged scapulae The gait is waddling and awkward and difficulty is experienced in rising from a lying to a standing position To do so the patient must roll over into a prone position with the face downward raise the trunk on the arms and knees and then "climb" up on himself by pushing his body upward by means of his hands, placed at increasingly higher points on his legs When he rises to a standing position he must then straighten up the trunk in the same way With one hand on his knee he pushes himself upright the other hand placed on the midthigh continues the process and finally the upright position is attained The reaction of degeneration (loss of faradic response and changes in galvanic response) is not usually found in these muscles

Pathological Anatomy—Atrophic changes in the anterior horn cells and posterior columns occur There is an hypertrophy of the interstitial tissues of the peripheral nerves and an atrophy of muscles and increase in fibrous connective tissue in them

Treatment—None other than symptomatic

Hereditary Primary Optic Atrophy

Synonym—*Leber's disease*

Definition—Slowly progressive primary optic atrophy and blindness, occurring as an hereditary disease and beginning about the age of puberty The condition is rare

Infections of the Nervous System

It is frequently difficult to define whether a disease of the nervous system is degenerative or inflammatory or toxic in nature Inflammatory and degenerative changes exist side by side and frequently the etiological agent cannot be determined The differentiation becomes even more difficult when one attempts to separate the inflammatory disease into those of infectious origin and those which are not infectious

Syphilis of the Nervous System

Incidence—It has been stated that some manifestations of syphilis are found in 10 per cent of autopsies and that 15 per cent of all nervous diseases are syphilitic in origin (Grinker) In cases of syphilis of the nervous system it is often impossible to obtain a history of primary infection as primary and secondary manifestations may be absent or escape notice It seems in fact that the occurrence of secondary skin lesions diminishes the incidence of involvement of the nervous system and, conversely, that the absence of skin *lesions increases the likelihood of cerebrospinal syphilis The disease is more* common in males than in females and it is possible that alcohol and trauma may predispose to its occurrence The possibility of trauma as a predisposing factor by diminishing local resistance is of medico legal importance but must not be accepted too readily Moore estimates that early involvement of the nervous system will occur about three times more often after inadequate or irregular treatment in the early stages than after no treatment at all On the other hand the incidence of late nervous complications is not increased by inadequate or irregular treatment Both early and late involvement of the nervous system is diminished by adequate treatment

In about one half of the cases the nervous system becomes affected within three years of the primary infection Tabes dorsalis and general paresis however develop later and frequently an interval of twenty to twenty five years may exist between the contraction of the disease and these complications The fact that the disease may spread to the nervous system within such a short time and that it may manifest no symptoms or signs other than changes in the cerebrospinal fluid is an indication of the importance of routinely doing lumbar puncture on patients under treatment During the first two years of

Peroneal Muscular Atrophy

Synonyms —*Charcot Marie Tooth* atrophy, progressive neural muscular atrophy

Definition —An hereditary type of muscular atrophy *involving the distal* segments of the limbs and associated with pathological changes in the spinal cord and nerve roots

Etiology —The disease is usually hereditary and familial, but *sporadic* cases occur No other etiological factors are known

Symptoms —The onset is usually about the age of puberty or before twenty years The course is slow and progressive The disability usually begins in the small muscles of the feet with atrophy and weakness Somewhat later the same manifestations appear in the hands The involvement of the muscles extends upward but the characteristic feature of the disease is that the spread is never beyond the elbows nor the lower third of the thighs The atrophy and weakness are restricted to these distal portions of the limbs Because of the involvement of the small muscles of the feet talipes develops and a pes cavus or equino varus deformity results Fibrillary movements and coarse tremors may occur and the tendon jerks are diminished or absent *Electrical excitability* of the muscles is usually altered with a diminution in *the response to* both faradic and galvanic stimulation Paraesthesia and sensory impairment may occur The appearance of the limbs is characteristic the fully developed proximal segments and the atrophied distal segments resemble an inverted, long necked bottle The symptoms occur symmetrically on the two sides In the siblings of a patient instead of the typical signs being present, the only evidence of familial nature may be deformity of the feet

Pathological Anatomy —There are degenerative and atrophic changes in the anterior and posterior nerve roots in the cells of the anterior horn and Clarke's columns in the cord and also in the posterior columns of the cord The muscles themselves are atrophied

Prognosis —The course is slowly progressive Improvement is rare but the progress may be arrested

Treatment —The only treatment is symptomatic physiotherapy for the *wasting* and weakness and special boots for the deformity of the feet

Hypertrophic Interstitial Neuritis

Synonym —Dejerine Sottas disease

Definition —A rare disease associated with thickened palpable nerves

Etiology —Other than that it occurs as an hereditary disease the etiology is unknown

Symptoms —In this disease also atrophy begins in the distal parts of the limbs and ascends Pains sensory loss and incoordination also occur Deformities of the feet and curvature of the vertebral column may appear Occasionally Argyll Robertson pupils nystagmus and cranial nerve involvement are also present The superficial nerves are hypertrophied and palpable but not tender

in which colloidal gold solutions are reduced by the higher concentrations of spinal fluid and not by the lower ones, the test cannot be used to differentiate the various types of neurosyphilis and may be positive in nonluetic conditions In general paresis and also in many cases of multiple sclerosis, the formula will be something like 5543200000 where 5 represents complete reduction Other types of curve are 0001223200 or 0000012234

Meningovascular Syphilis

Definition—In this type of neurosyphilis the chief involvement is of the mesodermal tissues, the meninges and blood vessels A further subdivision may be made into meningeal vascular and meningovascular types

Symptoms—The involvement may be primarily meningeal or primarily vascular or both Syphilitic meningitis may be acute or chronic and may occur at any time during the disease In most cases symptoms develop within three or five years of the original infection The acute and chronic types are essentially the same in character but vary in severity In the acute type all the signs of meningitis may be present The neck is stiff and painful on movement and there is a positive Kernig sign Headache is a prominent symptom and is usually worse at night Fever nausea vomiting, clouding of consciousness and delirium occur In chronic meningitis also headache is frequent is often worse at night and may be associated with tenderness on pressure of the skull Fever is less common but sometimes occurs and nausea and vomiting may be present Mental symptoms are frequent, they are more fulminating in acute meningitis and progressive in the chronic form Apathy confusion impairment of memory, and stupor are common These types of meningitis are usually basal although the infection may spread up over the vertex The most characteristic focal signs *are those of cranial nerve paralyses and the third nerves are particularly often* involved Anosmia, optic neuritis scotomata defects in visual fields, papilledema and secondary optic atrophy paralyses of ocular movements ptosis loss of the pupillary reflex to light paralysis of the muscles of mastication or of the face, tongue or palate, and nerve deafness may all occur, depending upon the nerves involved Convulsions either focal or general may be present and are sometimes followed by residual paralysis

The cerebrospinal fluid in these cases is under increased pressure, the globulin and total protein are increased The cell count is increased according to the acuteness of the process and may number from 10 to 20 lymphocytes to thousands per cubic millimeter The spinal fluid Wassermann is frequently negative in this condition and the differentiation from tuberculous meningitis may be difficult in the acute form

The vascular type of neurosyphilis is due to endarteritis of smaller or larger vessels The process may be a diffuse change which will gradually lead to occlusion of small vessels without prominent focal symptoms or the occlusion of a large branch most often of the middle cerebral artery with prominent focal symptoms These changes may occur at any time during the course of the syphilis and must be carefully excluded in cases of hemiplegia in young people below the age of forty or forty five years Indications of the diffuse involvement are headache, irritability mental changes and sometimes con

treatment the cerebrospinal fluid should be examined at least at six or eight month intervals Determination of the blood Wassermann reaction is not enough, as this may be negative while the cerebrospinal fluid Wassermann is positive There is much clinical evidence to support the belief that there is a neurotropic type of treponema which is particularly likely to involve the nervous system The high incidence of cerebrospinal syphilis in husbands and wives, and in patients infected from one source, is an indication of this It is important therefore that the families of patients with this disease be examined as well as the patients themselves

Types—Cerebrospinal syphilis has been divided into different types determined by the clinical and pathological findings In this section the following divisions will be made asymptomatic neurosyphilis, meningovascular syphilis, tabes dorsalis, general paresis, gumma, congenital syphilis It must be borne in mind that cerebrospinal syphilis can manifest itself by any group of symptoms and is not confined to the above clinical types The most common findings in all these clinical cases are the changes in the cerebrospinal fluid and of these the positive Wassermann reaction is the most typical This reaction is not positive in all cases, indeed in many it is negative In as many as 30 per cent of cases with positive spinal fluid Wassermann reactions, the blood will be negative so that examination of the latter alone is not sufficient When these reactions are negative, it is sometimes possible to render them positive by the administration of a provocative dose of an arsenical preparation Novarsenobenzol 0 3 or 0 4 gm, in 10 15 c c of sterile distilled water, may be given intravenously and the tests repeated in about five days

Asymptomatic Neurosyphilis

Definition—Evidence of involvement of the nervous system shown by changes in the cerebrospinal fluid without clinical signs or symptoms

Changes in the cerebrospinal fluid may occur at any time during the course of syphilis These may be increase in pressure slight increase in cells increase in globulin a positive Wassermann reaction and reduction of colloidal gold (positive Lange reaction) All or any of these may be present without abnormal signs being apparent on physical examination The normal cell count in the cerebrospinal fluid is from 0 to 9 lymphocytes per cubic millimeter and this number is often slightly increased in asymptomatic neurosyphilis Various tests exist to show the presence of excess globulin and the simplest of these is the Pandy reaction This is done by dropping cerebrospinal fluid into a test tube containing 5 per cent phenol solution As the drops descend in the phenol solution, they will turn milky white when globulin is in excess This test is a very sensitive one The reduction of colloidal gold in solution is a reaction depending upon the ratio of albumin and globulin present In carrying out the test colloidal gold solution is added to spinal fluid diluted with saline to different concentrations and arranged in a row of test tubes with the higher concentrations to the left Precipitation will take place in some tubes and not in others and the degree of this will vary so that a curve can be plotted Apart from the fact that a typical curve exists in general paresis

endothelial cells, and the elastic layer splits The vessel becomes occluded and is surrounded by an area of softening The meningitis is usually a diffuse leptomeningitis with infiltration with lymphocytes This may involve the spinal as well as the cerebral meninges The dura may become involved and thickened In late cases there is connective tissue proliferation and the pia arachnoid becomes thickened The meningitis is most marked at the base of the brain and spreads upward into the Sylvian fissures Small gummata are frequently present in the leptomeninges and about the blood vessels These are granulomata made up of a dense accumulation of fibroblasts, lymphocytes and plasma cells New blood vessels form in them and the center breaks down becomes necrotic and filled with fibrous tissue The inflammatory process in the meninges and the occlusion of blood vessels cause softening and degeneration within the nervous parenchyma

General Paresis

Synonyms —General paralysis of the insane dementia paralytica

Definition —The most serious type of neurosyphilis, caused by direct extension of spirochetes to the nervous parenchyma and manifested by mental and physical signs

Symptoms —This is a late complication of syphilis which usually develops from ten to twenty years after the original infection The symptoms can be divided into mental and physical groups Males are affected about four times as often as females

Mental Symptoms —These may begin insidiously and progress for some years before their full significance is appreciated or they may be marked from the onset They may be described under the headings of intellectual changes delusions and affective disorders although these designations do not define different types of general paresis The first indication of impairment of mental ability is usually difficulty in carrying on business matters or work as efficiently as before This may be attributed to the age of the patient or to some other factor and its gravity may be missed The intellectual change is a gradual deterioration which may progress to dementia The patient becomes careless and inefficient about his work he is less trustworthy and becomes forgetful inattentive and unable to concentrate He has a poor comprehension of details and loses his ability to deal completely with matters of ordinary routine His judgment becomes impaired so that he is likely to lose money or to undertake contracts which he is unable to fulfill He commits himself cheerfully to the expenditure of sums far beyond his means and because of this may become involved in legal suits He grows careless about his habits and personal appearance will neglect to wash or shave or wear clean clothing Sometimes he may develop a Korsakoff s syndrome with fabrication to make up for his deficient memory of recent events Finally he may become disoriented demented bedridden and completely unable to look after himself Sometimes sexual excesses and perversions are present and may require restraint of the patient

As these intellectual changes are progressing delusions may appear Those described as typical of the condition although they do not by any means

vulsions When larger vessels are involved, focal symptoms appear such as hemiplegia, bulbar paralysis and pseudobulbar paralysis Of these by far the most common is hemiplegia which may take a few days to develop and is likely to show considerable improvement It is due to involvement of the pyramidal tract, usually in the internal capsule, and shows the signs discussed on page 987 *Occlusion of branches of vessels to the medulla may cause soften* ing there and paralysis of cranial nerve nuclei The resultant symptoms are dysarthria, dysphagia and dysphonia, from weakness of tongue, palate, pharynx lips and vocal cords The speech becomes unintelligible, because of the defect in articulation and not in higher speech functions Swallowing is difficult and fluids regurgitate through the nose In severe cases the patient may be unable to clear the mouth, throat and trachea of mucus and saliva, the mouth hangs open and the tongue is heavily coated Pseudobulbar paralysis is due to paralysis of the upper motor neurone components of these cranial nerves and produces dysarthria usually bilateral pyramidal tract signs and emotional instability In these cases of vascular syphilis both the blood and spinal fluid Wassermann reactions may be negative The globulin in the fluid may be slightly increased and there may also be a slight increase in the number of lymphocytes

The most characteristic single physical finding in cerebrospinal syphilis is the Argyll Robertson pupil This has already been discussed on page 1002 The typical Argyll Robertson pupils are contracted unequal on the two sides irregular, and inactive to light but active on accommodation All these changes are not present in all cases and the pupils may be equal and regular but inactive to light or irregular and unequal and sluggish to light It has already been mentioned that tonic pupils which react very slowly, so slowly that the reaction may be missed do not indicate syphilis, but these are rare As they may be associated with loss of knee jerks the resemblance to syphilis is all the closer (Adie s syndrome) In the presence of any of the abnormalities described above, syphilis is the first cause to be considered and the patient must be very carefully investigated

Meningovascular syphilis may also affect the spinal cord and cause soften ing by vascular occlusion and extension of the inflammatory process The condition is then called myelitis or meningomyelitis It usually occurs in the thoracic region and causes a spastic paraplegia (upper motor neurone paralysis of the legs) and sensory impairments up to the level of the lesion Root or girdle pains are common because of involvement of the posterior nerve roots by the meningeal inflammation Retention of urine followed by incontinence frequently occurs The cord lesion may be severe enough to cause the signs of transection of the cord with a flaccid paraplegia being followed by increase in tonicity and flexor spasms of the legs On the other hand the only physical signs may be those of bilateral pyramidal tract involvement The changes in the cerebrospinal fluid are the same as those described above with some times in addition the signs of subarachnoid block on manometric tests

Pathological Anatomy—The changes in the blood vessels are primarily those of an endarteritis The adventitia and media are infiltrated with lympho cytes and plasma cells there is proliferation of the intima and sometimes of the

tricles are larger than normal and the subarachnoid space is widened The con volutions are atrophied and small and the sulci are widened these changes are usually more marked in the frontal lobes The ganglion cells show different stages of degeneration and some disappear so that the cyto architectonics are altered The pia arachnoid is opaque and thickened and infiltrated with lympho cytes and plasma cells The dura may also be thickened and adherent and show evidence of a hemorrhagic pachymeningitis There is ependymitis of the ven tricular walls which become granular in appearance The perivascular spaces become densely infiltrated with lymphocytes and plasma cells There are patchy areas of demyelinization, and degeneration may also descend into the



Fig 404 —Spirochetes in the brain of a patient with general paresis (From Grinker (Neurology Courtesy of Charles C Thomas Publisher Springfield Ill)

spinal cord Fibrous glia proliferate to form a dense meshwork in the cortex and along the infiltrated vessels and ameboid glia are present The microglia also increase and form rod cells which are characteristic of this condition In about half the cases spirochetes can be demonstrated in the cortex and sometimes in the ganglion cells (Fig 404) Very characteristic of paresis is the presence of iron in the perivascular spaces adventitial tissue microglia and free in the brain The signs of meningovascular syphilis may also be present in general paresis

Prognosis —The prognosis of general paresis has been greatly altered by the newer forms of treatment especially fever therapy Untreated cases die

occur in all cases, are delusions of grandeur The patient believes himself to have unlimited power and wealth, he regards himself as the author or engineer of tremendous projects and he busies himself by acting in accordance with these delusions Frequently he will buy large numbers of things for which he has no need, and cannot pay and will distribute largesse to all with whom he comes in contact He becomes a nuisance to those in charge of him and to unsuspecting shopkeepers who are the recipients of his orders All this is carried out with a show of tremendous energy and with a cheerful expansiveness These patients are often euphoric and have an unjustified sense of strength and of well being Even when quite ill they will state that they never felt better and that they are doing wonderfully well Delusions of the infidelity of a marital partner are also common Hallucinations are not common in this disease

Affective disorders, or disturbances of mood, occur commonly The patient may be depressed worried anxious or agitated, or, on the other hand excited and maniacal At the beginning of general paresis there may be good insight on the part of the patient but this disappears in more marked cases so that they have no appreciation of their conduct as abnormal

Physical Signs —These may be present before mental changes become apparent or they may be absent even in the presence of mental changes They may vary considerably and may consist of signs of tabes dorsalis as well as of general paresis and the condition is then called taboparesis The facies is often vacant and smoothed out and there is frequently a silly smile or grin upon it Argyll Robertson pupils or some of the features of them usually occur The speech is slow and slurred and some syllables are left out or run together Tremor of the face, lips tongue and fingers is usually present and may interfere with such movements as those of writing, which becomes shaky and uneven In addition letters or syllables may be left out of written words just as they sometimes are out of speech Impairment of power may develop and sometimes apoplectic attacks with hemiplegia, and the usual signs of upper motor neurone lesions occur The tendon jerks are usually increased, but, if some tabetic manifestations are present as well the knee and ankle jerks are absent The plantar response will be extension if hemiplegia has occurred and sometimes also without gross disturbance of power Epileptic attacks, either focal or general, are not uncommon Ataxia with impairment of gait, optic atrophy and incoordination of arm movements may be evidence of a combination of tabes and paresis Loss of sphincter control and uncleanliness are evidences of the mental rather than the physical conditions

The cerebrospinal fluid is under slightly increased pressure and the lymphocytes are increased but not usually beyond 100 per cubic millimeter The total protein and globulin are both increased and colloidal gold solutions are reduced in the first zone and reported as 5554321000 or a similar formula This same type of Lange curve occurs in about half the cases of multiple sclerosis The cerebrospinal fluid Wassermann is positive and the blood Wassermann almost always the same

Pathological Anatomy —In general paresis pathological changes in the brain are widespread The brain is atrophied and shrunken so that the ven

rived In addition to the changes in position and vibration sensibility there are also abnormalities of pain sensibility Deep pressure pain is frequently lost so that squeezing muscles, or the tendo Achilles or the testicles, will not evoke pain In some cases fractures of the leg have been sustained, impacted and gone unnoticed until accidentally discovered on examination Superficial pain sensibility also becomes impaired in certain characteristic areas These are over the bridge of the nose on to the cheeks in the shape of a butterfly across the chest from the level of the second rib to the costal margin, on the inside of the arms and forearms, on the outer border of the legs below the knee, on the feet and in the perianal region In these locations apart from diminution in pain sensibility there may be a marked delay in its appreciation so that if the skin is pricked with a pin several seconds elapse before the pain is felt by the patient Other forms of superficial sensibility may or may not be impaired later

Normal equilibrium at rest and on movement is a function which requires both sensory and motor integrity To carry out voluntary movements properly, we must be able to will them, to move the parts to coordinate the movements and also, through position sensibility to know at each moment whether the desired movement is being carried out and also at what stage of its execution it is Sense of position consequently must guide us at all times and must be there to inform us that the movement we wish to do is being done Without this guide we can still carry out movements fairly well if we watch the parts involved and see that they are doing their jobs properly but this method is not as quick nor as efficient as muscle and joint sense With loss of sense of position therefore there is impairment in motor function and this type of impairment is ataxia

The first evidence of this ataxia is usually an unsteadiness in walking and turning and this is worse when the eyes are closed As it progresses the patient attempts to compensate for it by walking with the feet widely separated by raising the feet higher from the ground than normal and by bringing them down violently on the surface that is being walked upon The disability is worse in the dark when vision cannot be used as an aid and the patient will sway and stumble and perhaps fall Gradually one stick will have to be used then two and finally walking becomes impossible While this locomotor ataxia is developing there are also other evidences of ataxia If the patient is told to touch the nose with the finger he will be able to do so with his eyes open but not when they are closed and he must be guided by sense of position alone The same difficulty is experienced in placing one heel on the opposite knee If he is told to stand with the feet together and the eyes closed he will sway unsteadily (Romberg s sign) and the same thing will be noted as he stands before a wash basin and covers his face with his hands as he washes Voluntary movements consequently become much impaired but in addition, involuntary irregular jerky movements may occur of which the patient is not aware unless he sees them If he is asked to hold the arms outstretched and still it will be found that if he closes his eyes the arms and fingers will move irregularly

within two or three years. With malaria treatment it is possible to obtain remissions in 30 to 40 per cent of cases whereas spontaneous remissions occur in only 10 to 20 per cent.

Tabes Dorsalis

Synonym.—Locomotor ataxia.

Incidence.—This occurs more often in males and, as in other forms of cerebrospinal syphilis, there may be no history of primary or secondary manifestations of the disease. It usually occurs years after the initial infection just as does general paresis.

Symptoms.—While certain definite symptoms are characteristic of this disease, many atypical symptoms may be present in an individual case. As the disease involves principally the posterior nerve roots and their fibers which ascend in the posterior columns, sensory disturbances are a prominent feature of the symptomatology.

Pain may be the first symptom of which the patient complains and its significance may be missed for a long time during which it is vaguely labelled "rheumatism." At first the pain may be dull and aching but eventually it assumes the character of "lightning pains." These are severe, knifelike pains, which are felt chiefly in the legs but may occur in the arms or face. They may occur daily or in attacks lasting for some days or weeks and then followed by a period of relief. They are worse at night and in cold, damp weather, and they are also aggravated by constipation and intercurrent illness. The patient describes them as if a knife or a hot bar were shoved into his skin at right angles and deep into the flesh. The pains may remain at the same spot for a time or may jump about and they sometimes leave the skin reddened or ecchymotic. Each pain lasts but a few seconds but they occur in paroxysms. Girdle pains and root pains also occur and are severe. They follow the distribution of posterior nerve roots either around the body like a belt or down the limbs. They occur also in attacks, but in the interval there may be a constant feeling of tightness in the same segmental distribution. Paraesthesias occur and the common ones are a feeling of cold and numbness or the feeling that one is walking on wool or a carpet. These paraesthesias frequently occur across the chest and on the inside of the hands and forearms. In addition the patient may be aware of diminished sensibility or his skin may be hypersensitive to tactile and thermal stimuli. These sensory disturbances are probably due to irritation of the posterior roots by inflammatory reactions in the meninges.

Sensory losses are most marked for those types of sensibility which traverse the posterior columns. This impairment usually occurs in the legs but may begin in the arms in cases of so-called "cervical tabes." Vibration sensibility, position sense and sense of passive movement are impaired. The vibrations of a tuning fork placed upon a bony point will not be felt and passive movements of the toes or other segments of the limbs cannot be appreciated unless seen. Because of this loss of position sensibility the patient is ataxic and it is from this symptom that the name locomotor ataxia is de-

swollen, and there is an increase of synovial fluid *The articular surfaces* erode and atrophy and at the same time proliferative changes occur and loose bodies appear in the joint The result is swelling, subluxation, and marked *deformity* The knee joint is most often involved, but the condition may occur in other joints as well It is usually painless The same type of arthropathy may occur in syringomyelia

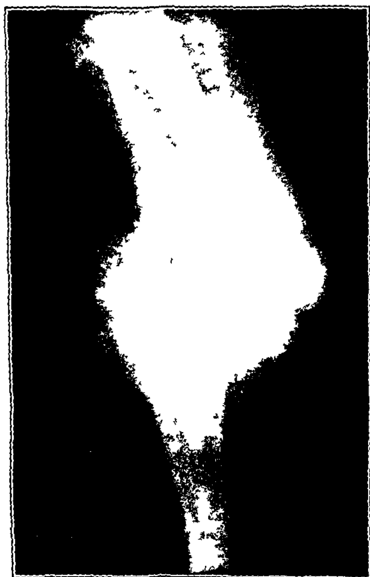


Fig 405 — A Charcot knee joint in a case of tabes dorsalis

Mental symptoms may occur in tabes and frequently a combination of tabes and paresis exists and is known as taboparesis *In addition signs of* meningovascular syphilis may be present though this is uncommon

The foregoing signs and symptoms are those of typical fully manifested tabes dorsalis As in all other diseases atypical forms exist and all the symp

It was stated earlier in this chapter that the preservation of tone depends upon the integrity of the reflex arc. It was noted that lower motor neurone lesions by breaking the efferent pathway of that arc diminished or abolished tone. In tabes dorsalis the afferent pathway of the arc is broken and again tone is diminished or abolished. Because of this, hypermotility of the joints is possible, the hip can be fully flexed on the abdomen and the knee can be hyperextended. In many old tabetics the legs are bowed, with the concavity forward, because of this hyperextension of the knee, and when tonicity is tested, the surfaces of the knee joint can be actually felt to bounce against one another and to rebound. Again because of a break in the afferent pathway of the reflex arc the tendon jerks are at first diminished and then lost. As tabetic signs are usually more marked in the legs, the tendon jerks may be abolished only in them and not in the arms. In the process of becoming diminished, they may be unequal on the two sides. The superficial reflexes are not altered.

The Argyll Robertson pupil is characteristic of tabes and occurs almost always in this form of neurosyphilis. Primary optic atrophy occurs frequently and may become complete so that blindness supervenes. It has frequently been noted that when optic atrophy develops ataxia in the extremities does not occur or does not become marked. Paralysis of external ocular movements of the sense of smell and of hearing sometimes occurs.

Disturbances of bladder function are common. At first this is usually retention so that the patient may go for many hours without voiding. It is found on cystoscopic examination that the bladder is relaxed and thin and that the posterior urethra is insensitive. Later dribbling begins to occur and finally there is complete incontinence. Sexual impotence also occurs frequently.

Crises are a particularly disagreeable symptom of tabes. They are pains referred to an organ of the body, usually the stomach. They may occur periodically or at irregular intervals, and they begin and end suddenly. *Gastric crises* consist of intense sharp abdominal pain which may be continuous or intermittent. The patients cannot eat or drink and if they do they vomit. Even without eating or drinking there is constant retching and the regurgitation of bile stained gastric contents. Such an attack may last for hours or days. Rectal crises consist of pain in the rectum, a constant desire to defecate without results, and tenesmus. Bladder crises consist of pain in the bladder and a constant desire to micturate, and laryngeal crises consist of pain in the larynx, cough, dyspnea and stridor. Many laparotomies have been carried out because of mistaken diagnoses in cases of gastric crises.

Trophic disturbances may be present in tabes because of the disturbances in pain sensibility. Perforating ulcers of the feet occur on the sole on the ball of the big toe. They may begin as a callus which breaks down to form an indolent chronic ulcer. This is small and circular and may extend deeply enough to involve the bone in an osteomyelitis. Fractures may occur without pain and heal slowly with an excess of callus formation. Bed sores are particularly likely to occur in bedridden incontinent patients. A particular type of arthropathy known as Charcot joint (Fig. 405) is a not uncommon complication. This may follow a slight trauma. The joint becomes

convulsions are usual, and there is frequently some hydrocephalus although this does not lead to deformity of the head like infantile hydrocephalus Pupillary abnormalities such as the Argyll Robertson pupil, optic atrophy cranial nerve involvement, hemiplegia and diplegia and disturbances of growth and nutrition are common The paretic form may first manifest itself between the ages of ten and fifteen years, and it follows a slow course Tabes dorsalis may not be evident until early adult life The blood Wassermann is almost always positive, and the cerebrospinal fluid shows the same changes as in acquired syphilis The prognosis is poor

Treatment of Neurosyphilis

The treatment of neurosyphilis is an individual problem and has to be varied to meet the requirements of the particular case It is carried out in courses depending upon the type and severity of the syphilis and the general health and physique of the patient The chief agents used are metallic preparations, penicillin and the induction of fever The metallic preparations their dosage the mode of administration and the undesirable reactions which may follow the use of these preparations are discussed in Chapter XIX The reactions which are of particular importance from the standpoint of neurology are the Herxheimer reaction and the ocular complications following the use of tryparsamide The Herxheimer reaction follows the activation of the syphilitic focus and the liberation of toxins due to intensive treatment with arsenic or penicillin It follows soon after the beginning of treatment and the signs will depend upon the situation of the activated focus and the structures involved by the toxins They may be generalized or they may be focal such as the paralysis of a cranial nerve or hemiplegia Tryparsamide frequently causes subjective blurring of vision and sometimes optic atrophy This is a serious complication as blindness may ensue The drug should consequently not be used in cases of optic neuritis nor of partial optic atrophy and during its use the fundi should be examined regularly A special technic for the administration of arsenic is the Swift Ellis method This is not used a great deal and any special benefit which it may have seems to apply to cases of developing optic atrophy and severe lancinating pains The technic is complicated and need not be discussed here but the treatment consists in the administration of salvarsanized serum into the subarachnoid space in the lumbar or cisternal region

The use of fever treatment in paresis and taboparesis is a decided therapeutic advance It should be used as soon after the diagnosis is made as possible The most efficacious means of inducing the fever is by the inoculation of malaria The malarial blood of one patient is given to another and after a variable incubation period the second patient develops the malaria The tertian type is ordinarily used and the injection of blood may be given intravenously or subcutaneously The best time to take blood from the one patient is immediately before a paroxysm If the administration to the second patient is to be intravenous 1 5 c c of blood are used while if it is to be subcutaneous about 10 c c are used In the former case the blood may be citrated but in the latter case if the transfer is to be made immediately this

toms of the disease need not be present The picture outlined above was common 30 years ago, but it is surprising how seldom a typical tabetic is encountered today Most of the present day tabetics have few signs in addition to Argyll Robertson pupils, absent knee and ankle jerks some ataxia, some pains and changes in the cerebrospinal fluid Whether this is an indication of the efficacy of the treatment of the past fifteen years, whether it is due to attenuation of the treponema or whether it is due to changes in our mode of living, it is impossible to say

Pathological Anatomy —The posterior nerve roots are smaller than normal and there is marked degeneration of the fibers ascending in the posterior columns As fibers from the lower thoracic and lumbosacral regions are chiefly affected and as the fibers in the posterior columns are pushed medially as they ascend, the degeneration in the cervical region is chiefly in the column of Goll and less so in the column of Burdach In the area of degeneration there is dense gliosis The blood vessels are small and sclerotic and the pia arachnoid is thickened In addition pathological changes have been described in other structures of the cord

Prognosis —This varies considerably The disease is not often rapidly progressive and many cases do not advance to a point of incapacity The response to treatment is also variable and some patients show considerable improvement In some the course is arrested, while in others there is a progressive advance in the symptoms

Gumma

Gumma of the brain is the rarest of the nervous manifestations of syphilis, and it is the rarest type of cerebral tumor (Grinker) Multiple small gummata occur in meningovascular syphilis, but large isolated gummata sufficient to cause symptoms of an intracranial tumor are very rare When they do exist they arise from the meninges and grow into the brain Their signs are those of an intracranial tumor with the general manifestations of increased intracranial pressure and focal signs depending upon their location As they respond but slowly to antiluetic treatment operation may be necessary to save the eyesight of the person They occur also in the spinal cord A positive Wassermann reaction and signs of intracranial tumor are not sufficient to make a diagnosis of gumma of the brain, as both syphilis and tumor may coexist, and sometimes in tumor of the brain there is a weakly positive Wassermann reaction in the spinal fluid

Congenital Syphilis

Congenital syphilis and its treatment will be described in Chapter XIX The nervous system is frequently involved and may show signs of a diffuse encephalitis, meningovascular syphilis tabes dorsalis or general paresis The diffuse encephalitis occurs early in life is manifested by widespread acute signs, and terminates fatally convulsions are common in this condition The other types of congenital neurosyphilis are essentially like those in the acquired form The most common is the meningovascular type Mental deficiency and

MENINGITIS

Pachymeningitis

Definition.—An inflammation or infection of the dura mater

Etiology—Pachymeningitis may occur in syphilis It may be due to infection secondary to an osteitis of the skull or vertebral column, and it may follow head injury It is frequently associated with the formation of an abscess and this pathological condition is described later

Pachymeningitis Interna Hemorrhagica

Definition—This condition is really one of chronic subdural hematoma and will be discussed under that heading (see page 1102)

Leptomeningitis

Before considering the specific types of leptomeningitis the general symptomatology of this condition will be described The severity of the neurological symptoms will depend upon the acuteness of the pathological condition in the meninges and the general systemic symptoms will depend upon the type and acuteness of the infection which is responsible for the meningitis The characteristic symptoms of acute meningitis are headache stiffness of the neck retraction of the head positive Kernig and Brudzinski signs and the presence of the products of inflammation and frequently also the etiological agent in the cerebrospinal fluid Such meningeal irritation may occur from infection inflammation and the presence of foreign substance such as blood in the subarachnoid space Kernig s sign is inability to extend the lower leg completely when the thigh is flexed at right angles or more on the abdomen *Brudzinski s sign is a flexion of one leg when passive flexion is made of the* other or flexion of both legs when the neck is bent forward on the chest In severe cases irritation may be sufficiently great to cause marked hyperextension of the entire body a condition known as opisthotonos In addition to these nonfocal signs of meningeal irritation there may be signs of focal involvement of the cranial nerves or of cortical centers in the brain Consequently in acute leptomeningitis headache photophobia vomiting fever slow pulse convulsions and signs of cortical irritation or depression are frequent

Specific Infections of the Meninges

The specific infections of the meninges may be caused by an invasion of bacteria or allied agents These usually are conveyed to them either by the blood stream or by direct contamination through the lymphatics or contiguous destruction of tissues The symptoms produced by these infections have been described above and the technic of lumbar puncture was described on page 1025 The specific infection may be identified by staining and bacteriological *methods or shrewdly suspected by more indirect methods* There are few forms of meningitis that are in any manner specific infections as the majority are due to organisms which may be said to involve incidentally or indirectly these tissues as part of a general or local disease The more specific will be dealt with first

is not necessary Immediately following the injection of blood there may be a rise in temperature for 24 to 48 hours unless the blood has been typed beforehand The incubation period varies from three to twenty days or more and before the establishment of definite periodic chills there may be a continued, irregular fever for a few days Advanced age, cardiovascular renal disease and malnutrition are contraindications to this treatment The patient should have from 8 to 12 rises in temperature of 103° F or more After the chills have begun, rectal temperatures should be taken every two hours and during the chills every half hour If the systolic blood pressure falls below 80 mm of mercury or marked tachycardia is persistent, the treatment should be stopped The malaria can be stopped by the administration of quinine 0 3 gm three times a day and this should be continued for about two weeks After the treatment has been completed, the return of the patient to activity should be slow

Fever may also be induced by the intravenous administration of typhoid paratyphoid vaccine The initial dose of this is 50 million organisms in about one or more cubic centimeters of normal saline solution given slowly intravenously Successive doses will have to be doubled each time or even more greatly increased Better results may follow dividing the dose and giving the second fraction from one to three hours after the first Fever can also be induced by physical means by the use of short wave electrical apparatus, but this requires special equipment Of the various means of inducing fever malaria seems to have the best therapeutic effects so that the result must come not from the fever alone

Potassium iodide seems to be particularly of value in productive lesions and in gummata It is very soluble and can be dispensed in water and taken well diluted It may be given in doses of 1 0 gm three times a day, gradually increasing to a total of 12 gm a day or more In acute syphilitic meningitis much larger doses will be of value

The treatment of neurosyphilis by chemotherapy and antibiotics follows the same lines as that of syphilis in general (Chapter XX) But here again this at present is in such a state of transition and flux that opinion as to the best method to be employed seems to change almost monthly Although penicillin is now a favorite drug to use the best interests of the patient would be served by having a line of treatment outlined by a consultant or by referring the patient to a special clinic as in tuberculosis

In tabes dorsalis apart from medicinal treatment, reeducation may be of great value in enabling the patient to compensate for his impaired position sensibility and so to improve the ataxia We pay little conscious attention to our ordinary movements as sense of position takes care of their proper regulation and will inform us if they are not being properly carried out The tabetic can learn to compensate for the impairment of his sense of position by relearning consciously how to carry on his ordinary movements His walking sitting down and getting up etc will be greatly improved by relearning how to do them properly

depends upon the relative balance of immunity and virulence The symptoms may be present for a few hours or days and the infection progress no further, the true cause being unrecognized and the patient being a carrier (see p 1070) or they may persist for days or weeks and the same result occur On the other hand, within minutes or in other cases delayed to hours, days weeks, and sometimes years, the infection may explode into a septicemic invasion

In conformity with many specific infections such as typhoid fever tuberculosis or syphilis, the protective barriers of the portal of entry may be overthrown and the infection become a *septicemia* or *bacteriemia* with all the general features of severe systemic prostration pyrexia leucocytosis and splenomegaly Here again the severity and duration of the symptoms are determined by the relative resistance of the host and the virulence of the invader The bacteriemia may last for a few hours or days or again for months without involvement of the meninges Recovery may take place promptly or after a period, or death may occur from the septicemia in a like order of time It is usual however, in the great majority of the septicemic cases for the meninges to be involved within forty eight hours

This development marks the third or *meningeal stage* All the symptoms and signs of meningitis as outlined above appear in rapid succession—headache apathy, irritability, rigidity of the neck, hypertonia, Kernig and Brudzinski signs opisthotonos convulsions, delirium and coma in their varying degrees of intensity The recognition of the anatomical lesion is now not difficult This stage may be called the localized or metastatic lesion of the bacteriemia similar to the arthritis of the gonococcus or the skin rashes or mucous patches of syphilis It is true that these three stages—nasopharyngitis bacteriemia and meningitis may not be clear cut and constant in their elapsed time and severity but they are in their sequence *It is the former variations which have led* to the following clinical classification It is given with some hesitance as it implies distinct types of disease rather than variations of sequential intensity

I *Regular type*—all phases relatively moderate—death or recovery six to fourteen days
II *Bacteriemic type*—general symptoms dominate the meningeal
III *Meningeal type*—cerebro spinal symptoms dominate
IV *Malignant or fulminant type*—death occurs in a few days—shortest reported five hours—most likely due to overwhelming septicemia even though meningeal signs may be present
V *Relapsing type*—recurring exacerbations or relapses of the infection
VI *Chronic type*—any of the above going on to a progressive *productive meningeal lesion which produces signs of* increased intracranial pressure hydrocephalus or cranial nerve palsies

Before proceeding with the consideration of the last two types it would seem best to deal with certain symptoms and signs which are not directly due to the meningeal lesion As one of its older synonyms—spotted fever—implies there are frequently skin manifestations These consist of purpura petechiae and a large macular lesion which varies from a yellow red to a pink red color The former appear soon after the onset, and the last about the third or fourth day They are significant of a systemic meningococcic infec

Epidemic Cerebrospinal Meningitis

Synonyms —Meningococcic meningitis, spotted fever

Definition —This is a form of leptomeningitis due to a specific infectious agent and is communicable, occurring both sporadically and in epidemics It was first described as a clinical entity by Vieusseux in 1805, and the causative agent, the meningococcus, was determined by Weichselbaum in 1887

Etiology —The cause of epidemic meningitis is the meningococcus which is a gram negative biscuit shaped diplococcus It is commonly intracellular and closely resembles the gonococcus in its morphologic, staining, cultural and biologic characteristics It is a specific for the cerebrospinal system as the gonococcus is for the genitourinary Both may be found in other sites of infection but these are exceptions rather than the rule They both grow best on dextrose media which contains defibrinated blood and at a pH of 7 6 to 7 8 There are four immunologic types of the meningococcus Group I conforms to the original strain of Weichselbaum while II is the parameningococcus of Dofter, and III is closely similar to I, and IV to II The importance of appreciating the fact that there are these different types will be referred to under Treatment

Incidence —Children are much more susceptible than are adults in whom, as a rule there is a high natural immunity The infection is widespread through the world having been reported from practically all countries but chiefly in the north temperate zones In large centers of population, particularly in North America there are constantly reported sporadic cases On the other hand the severest epidemics have occurred in rural districts The factors leading to epidemics are not known There is a rough periodicity occurring about every ten to twelve years For further details of its epidemiology, the reader is referred to works of Webber and Hirsch

The disease is found throughout the year, but is most prevalent in the winter and spring months This is accounted for by the closer contacts at these periods as the disease is conveyed by droplet infection and to the fact that this is the time of the year when the majority of such diseases spread in the population which may be more susceptible on account of the prolonged absence of the effective solar rays No age is immune Males are slightly more liable than females which ratio is made conspicuous through epidemics occurring in camps and barracks

Symptoms —The incubation period is commonly held to be from three to five days and the portal of entry is through the nasopharynx, where it is conveyed by droplets of secretion either from active cases or carriers The onset is acute with signs of a nasopharyngitis slight malaise headache and fever It has been customary to differentiate the cases into various clinical forms or types These are however artificial distinctions being really of no value and are apt to confuse a broad conception of the disease They really depend upon the severity of the three stages of the infection and the virulence of the organism which determines the clinical predominance of each

As the portal of entry is through the *nasopharynx* here will be found the initial symptoms These may be slight and frequently pass unnoticed *This*

Chronic meningococcus meningitis may be either a continuation of the acute form or through the development of productive lesions may be considered as complications or sequelae

(a) A purulent exudate continues in the arachnoid space for a prolonged period in spite of treatment The temperature remains high and meningococci persist The eventual outlook is favorable in adults unless mechanical or obstructive lesions develop These are most common in infants and young children but do occur occasionally in older persons It usually assumes the following form

(b) Chronic posterior basal meningitis The exudate is thick and organizing chiefly over the basal areas, although it may cover the vertex as well In the former situation it may lead to obstruction of either the interventricular foramina or the foramen magnum Either of these conditions leads to an internal hydrocephalus with the usual signs of bulging fontanelles and cephalic cry The head retraction and opisthotonos are progressive but the limbs instead of being flexed are extended and spastic There may be a continuous pyrexia or it may recur after a short interval with leucocytosis The spinal fluid may be clear and neither lumbar nor cisterna drainage is effective Ventricular puncture reveals purulent fluid which contains meningococci, and temporarily relieves the pressure The outcome is fatal in from six to eight weeks

(c) In milder cases where the vertex is principally involved and the ventricular obstruction is not complete a more chronic state with all the signs of increased intracranial pressure may ensue A fatal result is, however eventually to be expected

The other metastatic lesions of this systemic infection are not numerous and consist chiefly of arthritis iritis chorioretinitis panophthalmitis pneumonia pleurisy pericarditis and orchitis

The *complications* or sequelae are the result of the local metastatic lesions and are therefore most numerous in the brain and cranial nerves The occurrence of *internal hydrocephalus and increased intracranial pressure* have already been referred to Closely associated with these are papilledema and optic atrophy There may also be deafness, strabismus and signs of other cranial nerve lesions

Pathological Anatomy—The anatomical changes are almost solely confined to the meninges and these depend to a large extent upon the stage at which they are examined In the early stages—particularly in the fulminating septicemic cases the meninges may reveal no lesion In similar cases with early nervous symptoms there is usually only hyperemia of the pia arachnoid and subarachnoid with edema and serous exudate With the lapse of time the exudative process becomes more intense and profuse There is greenish yellow fibropurulent exudate concentrated along the sulci particularly over the base and cerebellar areas The parietal occipital, and frontal lobes are irregularly involved In the chronic stages the exudate becomes more fibrinous and organized Microscopic examination reveals no specific features There is a progressive hyperemia and polymorphonuclear infiltration with many meningococci and finally fibrinous depositions which predominate in the chronic lesions The ventricles are invaded by the inflammatory process and

tion and have no relation to the meningitis They occur where the infection is purely a bacteriemia At times the purpura may be so massive and deep as to lead to necrosis, and plaques of skin may be removed leaving an ulcerating area From these necrotic patches the meningococci may be grown The mucous membranes and conjunctivae may also be the site of these eruptions They are more common in epidemics than in sporadic cases Herpes about the lips and face occur in about 10 per cent of the cases, and appear usually between the fourth and seventh days Splenomegaly is common and a pronounced leucocytosis is constant It is of the polymorphonuclear type and may number up to 40 000 per c mm Pyrexia ranges from 102° to 103° F but in the most severe and fulminating cases is seldom above 100° F It is often accompanied by chills which are conspicuous when the bacteriemic stage is prolonged without meningitis Vomiting would be expected when there is an increase of intracranial pressure, but it is prominent in this infection without such occurring

The meningeal lesion is recognized not only by the characteristic symptoms and signs but more specifically by the changes in the spinal fluid obtained by lumbar or cisterna puncture The fluid contains large numbers of polymorphonuclear pus cells which may or may not contain meningococci and these may be found free single in pairs or in small groups Their early recognition is of the utmost diagnostic importance They may not be found in stained smears of the fluid It is imperative that cultures be made on proper media, the most favorable being beef infusion peptone agar containing 1 per cent dextrose and 5 per cent defibrinated blood at a pH of 7 6 to 7 8 The cultures should be made immediately or the spinal fluid kept warm as the meningococci are particularly susceptible to cold It is best therefore to make cultures at the bedside directly from the lumbar puncture needle when still inserted

The relative frequency of the acute types varies considerably under different conditions The regular type is the most common in epidemics as well as among the sporadic cases, although in the former these cases are on the average more severe and fulminating types increase in number as the epidemic progresses

Chronic recurrent meningococcus meningitis really consists of one or more relapses The patient recovers from the primary infection the spinal fluid being normal and then suddenly there is a return of fever and meningeal symptoms These recurrences result from small pus pockets forming in the subarachnoid space which is otherwise clear, and they rupture leading to a repeated diffuse meningitis The cause of their formation is not understood but it is probably due to an incomplete immunity or to poorly drained areas where the therapeutic agent has not ready access

These recurring attacks are usually relatively mild and the infection is readily overcome with proper therapy The intervals are usually a few days but may extend to weeks or months There are seldom more than two Occasionally a local productive lesion leads to internal hydrocephalus which for mechanical reasons is serious

incidence is greater in the younger decades but the relative mortality is not parallel The following comparisons from the Detroit epidemic of 1928 31 are instructive in this regard

AGES	MORBIDITY IN CASES	MORTALITY IN PER CENT
0 4	535	58
5 9	214	40
10 14	186	36
15 19	155	43
20 24	157	50
25 29	115	55
30 34	72	60
35 39	58	64
40 44	43	50
45 49	29	86
50 54	22	70
55 59	7	100
60 64	4	100
65	2	0

Endemic and sporadic cases are relatively mild although startling exceptions are met with The severity of the onset is not necessarily parallel to the future progress In fact it is unwise to offer an opinion on the early severity of the disease The most unfavorable features are early coma, convulsions or violent delirium and large purpuric areas as compared to petechiae Early recognition and prompt treatment are of the utmost importance in prognosis in common with these same qualifications in all infections where a specific therapy is available

The *course* of the disease has been indicated by the degree of the virulence the type of the symptoms and the progress into the chronic anatomic meningeal lesions

Treatment.—It may be taken for granted that all the usual measures indicated in an acute infection will be employed For the central and peripheral symptoms of cerebrospinal irritation hydrotherapy is helpful Warm baths with gentle friction bring about great relief as does at times an ice bag to the head But the therapy of the greatest importance is specific and the earlier and more intensively it is used the greater are the hopes of success This may be either by specific serum or chemotherapy There is inherent in serum therapy a difficulty which is not sufficiently appreciated In common with pneumococcic sera all preparations do not possess equal potency for each type of meningococci There is little doubt that many of the failures in serum therapy are due to using a product which is not specific It is regrettable that such is the case and that the specificity may not be more easily determined Therefore a polyvalent serum has advantages although a more concentrated type specific serum would naturally give better results

The sulfonamides (sulfadiazine or sulfamerazine) and penicillin have now practically replaced specific sera They can be used either by mouth or intravenously (see Chapter XX) and have conspicuously reduced the mortality It is not necessary to determine the type of the organism In fact any purulent meningitis should be so treated promptly after a lumbar puncture has demonstrated its character and the causative agent determined later This saves those first hours which are so precious for a successful result Furthermore

distention is common at autopsy The cortex may also be invaded as may the spinal cord as the lesion extends from the vertex to the cauda equina

Diagnosis—The diagnosis is divisible into three phases (1) *Carriers*—It must be appreciated that particularly in epidemics but also at other times persons may suffer from a mild and even negligible nasopharyngitis and hence harbor the meningococcus in the nasal and pharyngeal secretions In fact these mild cases of nasopharyngitis without further symptoms may compose the majority of those infected, and many of these become carriers They undoubtedly are an important factor in spreading the infection in epidemics It would be expected that there would be some local lesion to allow the persistence of the organisms, but this is not clinically recognizable These cases are most common in epidemics and among those exposed may number from 50 to 60 per cent, but the majority cease to be so in a few weeks' time There are a small number who continue in this state They can only be recognized by bacteriological methods, meningococci being found in cultures taken from the nasopharynx

(2) The *septicemic phase* closely resembles other forms of blood infection except for the occurrence of the purpuric rashes These, however, are common in other infections such as typhus fever, Rocky Mountain spotted fever bacterial endocarditis, gonococcic, streptococcic and staphylococcic bacteriemias, and the hemorrhagic forms of the exanthemata Therefore a positive diagnosis can only be arrived at by blood cultures In the fulminating cases death may occur before this is possible and consequently sporadic infections of this type are frequently overlooked

(3) The *meningeal phase* is to be differentiated from other forms of meningeal infection which are dealt with below In epidemics this is comparatively easy although occasionally a mistake is made through omitting to examine the spinal fluid A lumbar puncture should be done immediately in all cases with the slightest suggestion of meningeal irritation The technic of this procedure has already been dealt with The examination of the spinal fluid gives the positive evidence of this specific infection The cells are always polymorphonuclear and may number from a few to many thousands per c mm This of course applies also to other pyogenic infections The recognition of meningococci therefore is the sole means of making an absolute diagnosis This may be accomplished by smears alone but cultures should always be taken to determine the type of meningococcus present

The other meningeal lesions which may give difficulty in the differential diagnosis are influenzal meningitis in children, preparalytic poliomyelitis and meningismus in pneumonia whooping cough middle ear disease mastoiditis exanthemata and gastroenteritis The examination of the spinal fluid usually clarifies the diagnosis except in those cases where organisms are not recovered in cultures If there is a polymorphonuclear exudate it is best to give the meningococcus the benefit of the doubt

Prognosis—There are a number of factors to be taken into consideration in prognosis Of first importance is the age incidence Patients under one year of age and over thirty withstand the infection relatively poorly The

Prognosis—This is very serious the mortality being between 90 and 95 per cent

Treatment—The treatment has until recently been discouraging Attempts have been made to produce antisera both bactericidal and antitoxic without much success in human beings The introduction of sulfathiazole, sulfadiazine and streptomycin has ushered in an era of hope in the treatment of this disease (see Chapter XX)

Tuberculous Meningitis

In Chapter VI when tuberculosis of the lungs was considered, mention was made of tuberculous meningitis It is a metastatic lesion and in the majority of cases an old caseous focus will be found either in the lymphatic glands or the lungs In some the infection can be definitely traced to a localized caseous area in the brain or meninges the relic of a long past blood infection It may also be part of the distribution of a general miliary tuberculosis It is more common in children than in adults

Symptoms—The onset is as a rule rather insidious There are commonly prodromata in the way of listlessness, headache anorexia, irritability and loss of weight After a period the headache becomes more intense and there may be a sudden increase of the disability with vomiting and pyrexia and not infrequently convulsions Sleep is disturbed and the signs of meningeal irritation become apparent (see page 1065) The pulse is rapid respirations slightly increased, the spleen may be palpable and the child may cry constantly

In a few days to a week the clinical pattern changes from one of excitement to one of progressive apathy The vomiting and headache subside but the opisthotonos and contraction of the limbs are progressive with an occasional cephalic cry The abdomen is retracted and firm Signs indicative of cranial palsies develop such as irregular pupils, strabismus and optic neuritis The apathy progresses into coma although convulsions are not infrequent The eyes remain half open and the respirations are sighing with a progressive tachycardia although the body temperature may now be subnormal Signs of paralysis become more extensive and may include the face and limbs

In some cases particularly in adults the onset may be almost explosive in its suddenness and the course last but a few days In others it may be quite prolonged extending into many weeks These variations seem to be related to the severity of the infection and the distribution and extent of the lesion

As in all cases with the slightest suggestion of meningeal irritation, a lumbar puncture should be done at once In this infection there are distinctive features The fluid is under abnormal pressure which should be recorded It is usually clear but on standing in test tubes a fine veil like web or clot appears in a few hours This is almost diagnostic The cells may number up to 1 000 or more and are practically all lymphocytes in contradistinction to pyogenic infections The reducing substances are under 30 mg per cent the chlorides under 640 mg per cent and the proteins are increased Tubercle bacilli are most easily detected by examining the clot mentioned above This is floated on to a glass slide, allowed to dry and then fixed and stained

this treatment can be carried out under conditions where repeated lumbar punctures would be difficult It must also be appreciated that horse serum is a foreign substance in the meninges and is held by some to perpetuate meningeal irritation and dispose to chronic meningitis Sulfonamides do not have this disadvantage

General measures particularly indicated are absolute rest and prevention of external stimulation as far as possible Particular care should be taken with the lumbar and cervical regions to avoid excoriation and infection Sedatives are sometimes necessary and the best are chloral hydrate and bromides Lumbar puncture serves this purpose as it also relieves the headache When there are signs of increased intracranial pressure which are not relieved by this measure, intravenous glucose (50 per cent) injections control it temporarily

The convalescence should be carefully guarded The patient should be kept in bed for at least three weeks after all signs have disappeared and return to normal activity slowly and progressively

Prophylaxis —All articles and bedding in contact with the patient should be sterilized and a minimum number of persons should be permitted inside the room in order that the number of possible carriers may be reduced Those in attendance should live an isolated life and before they return to other duties it is well to ascertain by nasopharyngeal cultures whether they are free of meningococci Masks have been advocated but are likely to give a sense of false security so that important measures like washing the hands after contact with the patient and allowing handkerchiefs to be contaminated are neglected Strict medical asepsis is always to be enforced Vaccines have been used to a limited extent and seem reasonable, but prophylactic injection of antimeningococcic serum is useless and has the disadvantage of sensitizing a person to horse serum

Carriers when detected should be isolated until proved to be free of the bacteria by two successive negative cultures The majority of carriers are usually allowed to leave quarantine after two weeks as it is impracticable to maintain large numbers longer If a patient remains a carrier after his convalescence is completed, the family should be notified and all measures taken to promote his relative isolation within the home

Influenzal Meningitis

This is a meningitis caused by the *B influenzae* of Pfeiffer and is undoubtedly part of a general bacteriemia due to this organism It is most common in children under two years of age In fact it may be called a disease of infancy

The onset is sudden with vomiting stiffness of the neck, and pyrexia The signs of meningeal irritation gradually develop and assume great intensity with hyperpyrexia coma and convulsions Metastatic lesions similar to those encountered in *influenza* sometimes occur (page 109) The disease is not particularly prevalent in influenza epidemics but occurs sporadically

Diagnosis —The diagnosis rests entirely upon finding the bacilli in the spinal fluid which is usually cloudy and yellowish and contains about equal numbers of polymorphonuclear cells and lymphocytes A positive nitrite reaction is quite significant

Prognosis—The prognosis is always serious but with the methods of treatment described below, the prognosis is steadily improving

Treatment—Treatment is of little avail unless the diagnosis is made early This is accomplished by cisterna and lumbar puncture done at the same time and the spinal canal irrigated with normal saline An even better method is to irrigate through double trephine openings well forward in the frontal area toward the vertex With cisterna and lumbar puncture needles in position, the subarachnoid space is irrigated with normal saline first from the lumbar to the cisterna areas until the fluid is clear, and then from the trephine openings on either side to the cisternal outlet Ventricular irrigation may also be necessary The prevention of adhesions may be aided by the injection of air before the saline irrigation Chronic adhesive meningitis leading to internal hydrocephalus accounts for certain of the deaths As in the case of pneumococcal infections elsewhere sulfonamides (sulfadiazine) (see page 250) have practically replaced the use of specific horse or rabbit serum This is to some degree unfortunate, because, although chemotherapy has been spectacularly successful there are occasional cases where the severe toxemia can be conspicuously reduced by specific serum There are also instances where thorough drainage is definitely indicated

Streptococcal Meningitis

Meningeal infection with the streptococcus occasionally is found where no other clinical evidence of infection can be detected As with the pneumococcus this invasion must take place through some occult portal of entry and is most probably carried by the blood stream but what factors determine their localization in the meninges is not known

Symptoms and Signs—The symptoms and signs do not differ in any way from the pneumococcal form and the distinction rests upon bacteriologic findings in the spinal fluid

Prognosis and Treatment—The treatment of streptococcus meningitis has been greatly improved through the use of penicillin and sulfadiazine The primary source of the infection such as the mastoid should be treated if possible At frequent intervals once or more a day, the spinal fluid should be completely drained off This should be done slowly by drops and the lumbar puncture needle may be left in place for hours if necessary Fluids should be forced and sulfonamides and penicillin given as outlined in Chapter XX

Secondary Meningitis

Meningitis is not an unusual complication or sequela to certain primary lesions The principal local sources of such infections are the following

Acute and chronic otitis mastoiditis facial and scalp erysipelas septic scalp wounds cellulitis above the angle of the mouth suppuration in the orbit nose antra ethmoid frontal and sphenoid sinuses compound fracture of the base of the skull and infected emboli from the heart or suppurating pulmonary lesions such as a lung abscess and bronchiectasis

In addition to these local sources meningitis may be a metastatic lesion in general infections such as typhoid fever, undulant fever, gonorrhea diph

Another method is to place a cover glass in a Petri dish and pour in sufficient spinal fluid to several millimeters' depth In a few hours a similar clot will form on the cover glass which then is removed, dried, and stained Guinea pig inoculation must sometimes be resorted to

Pathological Anatomy—Tubercles and exudate are usually most abundant over the interpeduncular space, temporal lobes, the Sylvian fissures and the lateral surfaces of the hemispheres They may also be found through the whole of the cerebrospinal system Their detection in the choroid by ophthalmoscopic examination indicates a miliary lesion The ventricles are always distended and tubercles may be very abundant on the choroid plexus The lesion is typical of tuberculosis and may extend into the nerve tissue, particularly along the blood vessels producing an area of tuberculous encephalitis

Diagnosis—The diagnosis rests upon the clinical findings and the peculiar changes in the spinal fluid, particularly the predominance of lymphocytes in the exudate When the polymorphonuclear cells are numerous there may be confusion with influenzal meningitis In cases of acute syphilitic meningitis there may also be difficulty as in both a lymphocytic exudate is present and there is high protein with relatively few cells But here the reducing substances and the chlorides are normal or only slightly reduced and spinal fluid Wassermann is positive in 100 per cent of the cases

Prognosis—This is extremely serious A few cases have been reported as cured but they are so exceptional as to suggest a mistake in diagnosis although the introduction of streptomycin provides a ray of hope for the future

Treatment—The patient should be kept as comfortable as possible with sedatives analgesics and repeated lumbar puncture Until recently no treatment was of any avail but now streptomycin (see Chapter XX) has given reason for encouragement It should be given both intravenously or intramuscularly and by mouth There is a danger inherent in its intrathecal use namely that it seems to cause a severe foreign body reaction in the meninges when given after this manner

Acute Syphilitic Meningitis

This will be referred to when syphilis is discussed as a disease, but was taken up in this chapter in greater detail under Cerebrospinal Syphilis (see page 1053)

Pneumococcal Meningitis

Meningitis caused by the pneumococcus may occur quite independently of any other clinically detectable lesion although there must be some occult portal of entry The onset is usually quite acute with all the classical signs of intense meningeal irritation There is pronounced pyrexia polymorphonuclear leucocytosis and prostration

The cerebrospinal fluid rapidly becomes purulent with a greenish color It is thickish containing much fibrin The pneumococci are abundant and are readily detected in smears and cultures

Diagnosis—The correct diagnosis depends upon the evidence found in the lumbar puncture fluid and must be arrived at very early in the course of the disease for any hope of successful treatment

The cerebrospinal fluid is under slight pressure and contains lymphocytes which vary from a few hundred to several thousand per c mm There is slight increase of the protein content The fluid has always been sterile to ordinary cultural methods but a filtrable virus has been recovered as mentioned above

Diagnosis —The diagnosis rests between encephalitis, poliomyelitis, syphilitic meningitis tuberculous meningitis and the meningeal lesions sometimes found in infectious mononucleosis (see Chapter XIX) It may at first be difficult to make a clear cut diagnosis, but in a short time the condition is clarified by the prompt recovery of the patient

Prognosis —The prognosis is good as the mortality is nil and there are no residual paralyses or mental changes Treatment is symptomatic

Serous Meningitis

This is an indefinite clinical syndrome and is not clearly demarcated from its causes It is sometimes called "sterile meningitis" It is a symptom rather than a disease entity The characteristic findings are signs of mild meningeal irritation, increased intracranial pressure irregular pyrexia and leucocytosis The spinal fluid is rich in protein and there is a mild leucocytic reaction, but the fluid is always sterile

The conditions with which this reaction is associated are usually traumatic or vascular The more common ones are subdural hemorrhage at birth, cranial trauma (without fracture necessarily), cranial operations where there has been considerable removal of tissue with resulting cavity cerebral thrombosis infarction and edema as in nephritis the nephrotic state and certain blood diseases and hemorrhagic conditions such as thrombocytopenic purpura, scurvy and hemophilia It may also occur in cases in which there is infection within the skull itself such as in acute mastoiditis

It would appear that the meningeal reaction is the result of bloody or serous collections between the dural layers and is an irritative response The presence of pyrexia and leucocytosis are findings common to most visceral hemorrhagic extravasations or infarctions and are in no way specific to this condition

Diagnosis —The diagnosis rests upon the appreciation of the probable etiology and the elimination of all other causes of meningeal irritation

Prognosis and Treatment —The prognosis and treatment depend entirely upon the character of the primary lesion as the meningeal condition is of secondary importance and resolves spontaneously Lumbar puncture may relieve the intracranial pressure and its associated symptoms but should be used with caution and a full appreciation of the original condition

Chronic Adhesive Arachnoiditis

Definition.—Adhesions of the arachnoid and cystic collections of fluid simulating brain or cord tumor

Etiology —This is often obscure but the condition sometimes follows injuries and is sometimes inflammatory in origin

Symptoms —These are usually slow in onset and prolonged in course The cystic collections of fluid often simulate tumors in their symptomatology

theria, pneumonia, pertussis, influenza, malaria, actinomycosis, scarlet fever, rheumatic fever, syphilis, and the acute exanthemata

The bacteria most frequently found in these forms of meningitis are the streptococcus, staphylococcus, pneumococcus, diphtheria bacillus, typhoid bacillus, treponema pallidum and gonococcus

Symptoms and Signs —The symptoms and signs of meningitis due to these causes are similar to those in acute meningococcic infection The anatomic pathway of the infection is usually obvious or the systemic infection has already been identified before the meningeal symptoms develop In rare instances these may appear early and seem to initiate the infection

The specific cause of the meningitis is proved by examination of the cerebrospinal fluid The prognosis depends upon the virulence of the organism and massiveness of the infection It is usually very serious It must be appreciated that the finding of bacteria in the cerebrospinal fluid does not necessarily indicate a meningitis in a clinical sense It is not unusual to recover organisms of low virulence and in scant numbers in the lumbar puncture fluid with little or no cellular reaction in cases of otitis media mastoiditis, and meningeal thrombosis This may be an anatomical but not a clinical meningitis and recovery is the rule

Treatment —The treatment is the same as that outlined under Pneumococcic Meningitis If specific drugs or sera are available, they should be used early and persistently

Acute Lymphocytic Meningitis

An exudate into the cerebrospinal fluid is almost a constant finding in acute anterior poliomyelitis and in acute encephalitis During the first 24 hours or so the cells are polymorphonuclear but soon these are superseded by lymphocytes This cellular reaction undoubtedly signifies a meningeal lesion mild though it apparently may be

There have been reported during recent years in increasing numbers cases with meningeal symptoms in which there was a lymphocytic exudate in the lumbar puncture fluid It has been variously called *acute aseptic meningitis* by Wallgren *benign lymphocytic choriomeningitis* by Armstrong and Lillie *benign meningitis* by Rivers and Scott and other synonyms, but probably the best designation is *acute lymphocytic meningitis*

It has now been definitely demonstrated that this disease is due to a medium sized virus which has been found in the spinal fluid and blood during its acute stage Furthermore antibodies have been demonstrated in the blood of patients on recovery The disease has been transmitted to monkeys guinea pigs and mice House mice form a natural reservoir for direct or indirect human infection

Symptoms and Signs —The onset is sudden with intense headache epigastric and ocular pain nausea and vomiting pyrexia and signs of meningeal irritation such as stiffness of the neck and Kernig s sign There is pyrexia from 100° to 104° F which is irregular and lasts for a few days There is no paralysis and the reflexes are normal

and involvement of the pyramidal tract are sometimes present In cerebellar abscesses there may be slight or marked cerebellar signs The pain will frequently be located in the occipital region and down the back of the neck and the neck may be stiff Cranial nerve signs may occur from pressure on the brain stem Abscesses in other locations will cause focal signs depending upon the structures involved If the infection has not broken into the subarachnoid space, the spinal fluid will be clear, although its pressure may be raised The cells may be slightly increased, but not more than 100 per cubic millimeter, and the protein content may be raised When the infection has spread to the subarachnoid space the signs of meningitis will be present

Brain abscess may occur as metastasis particularly from lesions of the lungs such as bronchiectasis and lung abscess In these cases it is usually multiple and may create a most bizarre pattern of symptoms The diagnosis of brain abscess is frequently very difficult and especially the differentiation of cerebellar abscess from acute labyrinthitis without intracranial complication In acute labyrinthitis there are nystagmus to the opposite side past pointing to the side of the lesion with both hands and vertigo and falling to the side of the lesion In cerebellar abscess the nystagmus is to the side of the lesion, the past pointing is also to the side of the lesion but only with the homolateral hand, and there are vertigo and falling to the side of the lesion Past pointing is tested by having the patient raise and lower his arm in front of him When it is lowered it should be made to touch the finger of the examiner held in front of the patient After doing this several times with the eyes open the patient should then do it with the eyes closed but if it deviates to one or the other side as it attempts to touch the examiner s finger then past pointing is present

Brain abscess should be suspected in all cases of otitic inflammation in which the condition does not progress satisfactorily or in which it is complicated by increasing stiffness of the neck irritability somnolence pupillary changes congestion of the retinal veins pain in the homolateral side of the face and increasing headache These symptoms may occur to a less degree in serous meningitis (see page 1077) complicating inflammation of the mastoid or labyrinth

Pathological Anatomy —The infection that leads to the brain abscess is usually due to thrombophlebitis and not to direct extension From the veins it breaks into the cerebral tissue and may also spread by the perivascular spaces to involve the meninges Necrosis and polymorphonuclear infiltration take place and within three days compound granular corpuscles may be found The acute abscesses spread without encapsulation but the chronic abscesses are well encapsulated and surrounded by an area of softening The encapsulation is by connective tissue and not by glia At a distance from the chronic abscess there is often perivascular infiltration with lymphocytes and plasma cells which is probably due to filtration of toxins but not of organisms Although glia cells do not take part in the formation of the capsule they show degenerative signs in the neighborhood of the abscess

Prognosis —Metastatic abscesses are usually multiple, and because of this and of the fact that the primary source ordinarily cannot be treated the

but the signs are likely to be less marked and more variable In the brain the adhesions usually form at the base and cause hydrocephalus, increased intra cranial pressure, and sometimes cranial nerve palsies The condition often exists in contact with inflammatory processes going on in bone, as in the mastoid cells The involvement may be diffuse or local In the cord, signs of com pression are also manifested There may be pain in the back and vague motor and sensory impairments, but the level of involvement is not as well defined as in tumor cases On lumbar puncture there may be signs of block, and the use of lipiodol may be necessary to determine the level of the lesion

Prognosis—Following operation partial or complete recovery usually occurs

Treatment—Craniotomy or laminectomy with freeing of the adhesions and evacuation of the cysts

Other Types of Meningitis

Other organisms may also cause meningitis, but this occurs infrequently Bacillus typhosus, coli, enteritidis, dysenteriae, anthracis, the virus of mumps, streptothrix, leptothrix and yeasts, such as torula, have all been described as etiological agents

Intracranial Abscess

Definition—Abscess formation in the epidural or subdural space or in the brain substance

Etiology—The usual cause is spread of infection from the ears, mastoids or nasal sinuses Metastatic abscesses also occur from sources at a distance, particularly from the lungs The abscesses may be single or multiple (Fig 406) The bacterial cause will be the same as that of the primary infection

Symptoms—The onset of symptoms may be insidious and the diagnosis difficult It frequently follows suppression of discharge in a case of sup purative otitis media operation on the mastoids or an acute flare up of an infected ear The onset of symptoms may be acute or subacute Headache, vomiting malaise slight fever and changes in the personality and sensorium are suggestive signs The patient may grow irritable have periods of drowsi ness and of mental dullness There may also be a polymorphonuclear leuco cytosis in the blood Signs of increased intracranial pressure may occur, but of these, headache may be the only prominent one At first this may be par oxysmal but later it will become continuous and severe Papilledema is often slight or absent Slowing of the pulse is a common, but not constant finding As pressure and toxicity increase there may be delirium and coma

Epidural extension of the infection may cause no signs other than those already relating to the mastoiditis Headache and tenderness of the side of the head may be noted Extension beyond the dura from an ear or mastoid infection usually involves the temporal lobe or the cerebellum and in these loca tions, may not cause focal signs for some time If the lesion involves the left temporal lobe in right handed people there may be some aphasia Involvement of visual fibers passing through the temporal lobe may cause a quadrantic hemianopsia to the opposite side of the body Paralysis of ocular movements

involved nerve roots), sometimes herpetic eruptions in the same distribution and signs of compression of the spinal cord The cord signs are usually paraplegia and sensory loss, up to the level of the lesion, and impairment of bladder function The protein and cells in the cerebrospinal fluid are increased, and xanthochromia and Froin's syndrome (see later) may be present The Queckenstedt test may show evidence of a complete or partial block In cases of Pott s disease x ray examination will show the typical changes in the vertebral column The onset may be rapid

Pathological Anatomy —There is obliteration of the extradural space with pus which becomes encapsulated In the cord there is degeneration and there may be softening In Pott's disease the characteristic changes in the spinal column are present

Prognosis —This varies with the duration of the abscess and the damage to the cord The condition is always serious but with relief of the compression the outlook is not hopeless and considerable, or even total recovery may occur

Treatment —In Pott's disease the treatment is that ordinarily carried out for the spinal caries In nontuberculous abscess laminectomy and drainage should be done

ENCEPHALITIDES

During the past thirty years much attention has been devoted after a modern fashion to a group of diseases which are probably much older than is usually appreciated Among these may be included the following

1 *Epidemic Encephalitis* (synonyms—encephalitis lethargica epidemic neuraxitis type A encephalitis [Japan] epidemic stupor Economo s disease)

2 *Acute Disseminated Encephalomyelitis* (synonyms—postinfection encephalitis postvaccinal encephalitis postmeasles encephalitis acute perivascular myelinoclasis)

3 *St Louis Type of Encephalitis*

4 *Equine Encephalomyelitis*

All of these conditions show a strong clinical resemblance The specific differential diagnosis rests entirely upon the history the local occurrence of an epidemic or the isolation of a specific virus where known to exist It is unfortunate that the term "epidemic encephalitis" was applied to one of this group because others also occur in epidemics but 3 and 4 above were not then recognized

Epidemic Encephalitis

Definition —An infectious disease of the central nervous system which may involve any part and so present diverse symptoms A characteristic acute attack consists of lethargy and cranial nerve paralysis

Etiology —The etiology of this disease is unknown It is believed to be due to a virus and it presents the characteristics of an infectious disease Males and females are about equally affected It is most common in young adults

Symptoms —As this disease may affect any part of the brain and in some cases even the cord and peripheral nerves the symptomatology varies to a

prognosis is bad. Single abscesses offer a better prognosis with surgical treatment, but even then the death rate is high. Spontaneous recovery occasionally takes place.

Treatment.—The treatment consists of drainage after the abscess is localized. The primary source of infection, such as the mastoid or lung, should be dealt with first. The possibility of brain abscess developing in bronchiectasis or lung abscess is one of the important indications for early surgical interference in such conditions. If there is a gross tract of infection from the primary source to the brain abscess, the latter can be drained at the same time. If such a gross path of infection does not exist, then the abscess should be opened and drained through a clean field. Appropriate chemotherapy and/or antibiotic therapy should be employed, as the bacteria found in these lesions are usually sensitive to their action (see Chapter XX).

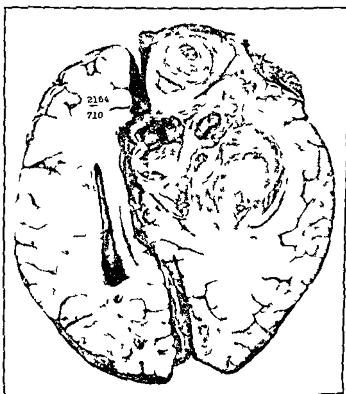


Fig. 406.—Multiple encapsulated cerebral abscesses.

Extradural Abscess of the Cord

Definition.—Intraspinal but extradural abscess causing compression of the spinal cord.

Etiology.—Epidural abscess may be due to Pott's disease of the spine (tuberculosis) or secondary to a pyogenic infection elsewhere.

Symptoms.—There are general signs of malaise and intoxication. The local signs are pain and tenderness of the back in the involved region. In Pott's disease there are in addition the signs of the spinal caries. Neurological manifestations consist of root pain (pains in the segmental distribution of the

that they must be institutionalized Occasionally insomnia persists as a sequela and is sometimes manifested only at night whereas during the day time the patient is drowsy and lethargic

2 Respiratory disorders These are not common, but are a very definite sequela of epidemic encephalitis They consist of marked dyspnea and slow noisy breathing They are not associated with any impairment of body function or oxygenation of the blood

3 Focal symptoms may persist when the disease has completely destroyed a part These are usually paralyses of some of the muscles supplied by the third nerve Occasionally, also muscles supplied by the bulbar nerves are paralyzed so that dysphagia or dysarthria may result Tremors choreiform movements, and torsion spasms also persist as sequelae or appear sometimes after the acute disease

4 Paralysis agitans or the Parkinsonian syndrome is the most common sequela of encephalitis lethargica Frequently an interval of years elapses between the acute attack and the appearance of the sequela, and in many cases the patient is unable to give a history of an acute attack The symptomatology of this condition is discussed later in the section concerned with vascular diseases of the nervous system

5 Oculogyric crises Oculogyric crises are a sequela which became appreciated some years after the epidemic of encephalitis which occurred from 1918 to 1921 These crises consist of forced conjugate movements of the eyes usually in an upward direction They occur at irregular intervals Sometimes they can be precipitated by moving the eyes in different directions but in other cases there is no precipitating factor known During the crisis the eyes will look upward and the patient will be unable to bring them out of that position Less frequently forced lateral conjugate deviation and also downward movements occur Some of these patients learn tricks by which to prevent or overcome this disability Thus keeping on the hat so that its brim will shade the eyes will prevent attacks in some cases In other patients attempts to read will bring the eyes back to a central position The individual attack may last from a few minutes to an hour or more These crises are frequently associated with other sequelae of this disease, particularly with the Parkinsonian syndrome

6 Diabetes insipidus also occurs as a sequela of encephalitis The symptoms and treatment of this disease are discussed on page 868

7 Obesity follows in some cases The diabetes insipidus and the obesity are probably due to involvement of the gray matter in the vicinity of the third ventricle

Pathological Anatomy—The brain is hyperemic and congested There may be hemorrhagic and inflammatory reactions in the meninges Perivascular hemorrhages and infiltration with lymphocytes occur in the brain substance and are most frequent in, and often limited to the midbrain and region of the basal ganglia They may extend elsewhere Cellular infiltration may extend beyond the perivascular spaces and be present in small foci in the brain substance Degenerative changes are found in the nerve cells and in the walls of the blood vessels

great extent It may be divided into symptoms due to the general infection and symptoms due to the focal involvement For some time previous to the manifestation of characteristic symptoms, the patient may complain of head ache diffuse pains and some drowsiness At the onset of the acute illness there may be fever but this is not usually high, may be intermittent and may persist for a long time Headache general malaise vomiting and constipation also occur Lethargy is one of the most characteristic symptoms Ordinarily the patient can be aroused and will answer questions but will then immedi ately fall back into a sleep Sometimes the lethargy is more marked and the patient sinks into coma The facies is dull, smooth and apathetic Mental symptoms may be present and at the onset of the disease they may be the only manifestation for some time Depression, maniacal symptoms and schizophrenic symptoms have all been described In addition, irritability restlessness and sometimes delirium may occur The cranial nerves are com monly involved and particularly the third nerve with the result that ptosis, strabismus, and diplopia almost always occur There may be alterations in the pupillary reflexes with loss of the reflex to accommodation and with in ability to converge the eyes on looking at a near object Other cranial nerves are sometimes involved including the sixth and seventh and the nerves arising from the medulla Abnormal movements are also a common symptom in this disease Tremors twitching myoclonic movements and chorea and athetosis may occur Sometimes hiccough may be a very troublesome symptom Dur ing the acute stage of the disease signs of paralysis agitans may be present, although these occur more commonly as a sequela The reflexes may be altered and may vary from day to day and in some cases there is evidence of pyramidal tract involvement Sensory loss is rare although pain and hyperesthesia do occur Sphincter control is abolished in some cases either as an evidence of delirium or coma or because of loss of control due to focal lesions Cerebellar signs and symptoms of cord involvement like those of anterior poliomyelitis occasionally are present Sometimes a syndrome simi lar to myasthenia gravis occurs Respiratory disturbances are sometimes present during the acute attack and sometimes occur as sequelae These may be dyspnea irregular respirations and deep sighing breathing The cerebro spinal fluid is clear it usually contains an increase in cells, ordinarily from 10 to 20 lymphocytes and rarely more than 100 per c mm The globulin may be increased a little the sugar is increased in contradistinction to meningitis in which it is decreased and some reduction of colloidal gold may occur

Course —The course of the disease is variable It may persist for a long time and relapses may occur The sequelae of epidemic encephalitis are of great importance and of considerable interest In many cases the sequelae over shadow the original attack which may have passed unnoticed The more common sequelae are the following

1 Personality changes These are especially common in children and young adults They consist of personality and conduct disorders and some times emotional and intellectual disturbances It is common to find a child who was previously circumspect in every way become an habitual liar or thief Frequently, also, they become quarrelsome difficult to manage and cruel so

son recently vaccinated, may be given intravenously or intrathecally with great benefit If this is not available, 10 c c of citrated whole blood may be given intramuscularly In encephalomyelitis complicating specific infectious diseases, 10 c c of convalescent serum, obtained from a person who has had the disease within the previous year should be given intramuscularly or intravenously

St Louis Type of Encephalitis

This type of encephalitis differs somewhat from the so called epidemic form although it may also occur sporadically or in epidemics It is characterized by symptoms and signs referable to the meninges and cerebral nervous system

Etiology—It is caused by a virus the mode of transmission being unknown although certain species of mosquitoes are suspected as experimental transmission has been affected by this means *In distinction from the epidemic form* it is most prevalent in the summer months whereas the former is more common in the winter Also although no age is exempt it occurs more frequently after forty five while the epidemic form is more usual before this age

The virus is filtrable 20 to 30 millimicrons in diameter and can be transmitted experimentally through mice and rhesus monkeys It can be grown only on media containing viable susceptible cells A similar summer epidemic encephalitis has long been recognized in Japan But this encephalitis differs from the St Louis type on immunological grounds

Symptoms and Signs—The onset may be abrupt or insidious For this reason it has been customary to classify it into three groups This hardly seems justified With the acute onset there is early high fever nausea vomiting headache neck rigidity vertigo and Kernig s sign all of which would indicate an intense *meningeal involvement* The signs indicative of central nervous system lesions are lethargy ataxia speech difficulty mental confusion and tremor of the tongue lips and hands Paralyses are not frequent and that of the eye muscles is rare The deep reflexes however may be exaggerated with the abdominal reflexes absent A bradycardia is sometimes conspicuous

When the onset is insidious the temperature gradually rises over three or four days with other symptoms and signs of a general infection such as malaise chilliness sore throat mild conjunctivitis and photophobia and generalized muscle and abdominal pains Finally the meningo encephalitic symptoms and signs appear similar to the cases with an acute onset

The spinal fluid reveals the usual signs of meningeal involvement it is under increased pressure it contains a variable number of mononuclear cells the globulin is increased it contains a normal amount of sugar and no bacteria are found

In an epidemic there are a fair number of quite mild cases which exhibit only some headache and moderate fever Many of these are undoubtedly overlooked when they occur sporadically and even *in epidemics unless a lumbar* puncture is done

Pathological Anatomy—On gross examination there are found edema congestion and hemorrhages in the brain and spinal cord The microscopic

Prognosis.—When the initial attack is very acute death frequently results. The involvement of the medulla oblongata is serious because of the risk of cardiac and respiratory failure. The sequelae of the disease, or at least those which cause the greatest disability, are resistant to treatment. The prognosis therefore is always doubtful, inasmuch as these sequelae may not make their appearance until years after the original disease.

Treatment.—There is no specific treatment for the acute attack. Isolation, nursing care, and symptomatic treatment are all of value. Personality changes and residual focal signs are usually permanent. Paralysis agitans may be improved a little but its treatment is disappointing. Diabetes insipidus can be well controlled by appropriate measures.

Acute Disseminated Encephalomyelitis

Definition.—An acute, toxic or infective disorder of the nervous system which may follow vaccination, certain of the acute specific infectious diseases (particularly measles and mumps) and other causes.

Etiology.—The term comprises a group of nervous disorders, which seem to be increasing in frequency, but the ultimate cause and pathology of which are unknown. The condition occurs after vaccination, in conjunction with or immediately following most of the infectious diseases, after antirabic inoculation, and sometimes as a spontaneous disease the cause of which cannot be determined. It is unknown whether the involvement of the nervous system is due to actual invasion by the virus of the specific disease, to the action of toxins liberated elsewhere by these organisms, or to a specific virus which invades the nervous system and becomes pathogenic in the presence of these other diseases.

Symptoms.—It is obvious that a disseminated inflammatory disease of such obscure etiology and pathology should manifest a multiplicity of different signs in different patients. The onset is usually acute, and headache and vomiting and fever are frequently present from the beginning. Drowsiness, stupor, delirium and coma may occur. Meningeal symptoms are present in many of these patients. There may be signs of widespread or focal damage to the central nervous system, and these signs will depend upon the structures involved. Cranial nerve paralysis, optic neuritis, convulsions, monoplegia, hemiplegia and trismus may occur in different combinations. The cerebrospinal fluid may be normal or may be under increased pressure, contain an excess of cells, and an increased amount of protein.

Pathological Anatomy.—The brain is congested and edematous. There may be degeneration of ganglion cells and typical areas of focal demyelinization, frequently arranged about blood vessels. Perivascular hemorrhages and infiltrations are common, and there may be perivascular and pericellular edema.

Prognosis.—The prognosis is variable both as to life and as to the persistence of focal residua. The mortality rate averages about 25 to 30 per cent but varies considerably.

Treatment.—Repeated lumbar punctures and the use of hypertonic glucose saline solution may diminish cerebral edema and intracranial pressure. In postvaccinal encephalitis 10 c c of immune serum obtained from a per

be more insidious and much less violent In all cases there are signs of meningeal irritation—rigidity of the neck and back and Kernig s sign In children an unusual edema of the face and arms is frequent

The spinal fluid is under increased pressure and contains many cells up to several thousands In distinction from other encephalitides the polymorphonuclear cells predominate up to 70 to 90 per cent As is common to most types of encephalitis there is an increased protein but normal sugar content A polymorphonuclear leucocytosis is almost constant

Diagnosis—Diagnosis of an encephalitis is comparatively easy from the clinical aspect but the type is another matter An epidemic associated with a similar outbreak in horses and/or mules is most significant but an absolute diagnosis can be arrived at only by the detection of the virus from brain tissue at autopsy The specific causal diagnosis therefore usually rests upon inference

Course and Prognosis—The course of those who recover is about ten days by lysis But the mortality is high particularly in children as it has reached in the few epidemics reported up to 70 to 80 per cent Death usually occurs in the first few days The sequelae in those who survive are serious consisting of severe physical and mental deterioration

Treatment—The prevention of the disease in an epidemic area can be resolved into measures to exclude the mosquito from contact with humans particularly children There is no known specific therapy as yet therefore symptomatic measures are the only ones indicated J C M

Diffuse Sclerosis

Definition—This term includes a variety of diseases of mixed degenerative and inflammatory nature It includes Schilder s disease or periaxialis encephalitis diffusa and also a group of familial cases described by Krabbe The clinical findings and outcome are the same in the different types but the etiological factor is unknown Whether the disease is due to a primary defect in nervous tissue or to a toxic or infective agent has not been determined

Symptoms—The usual age of onset is before puberty although some cases develop later Males seem to be affected more often than females The characteristic symptomatology consists of blindness, mental deterioration, and spastic paralysis of the two sides of the body The disease ordinarily begins in the occipital lobes and the resulting blindness is then not associated with pupillary changes or pathological manifestations in the fundi When the temporal lobes are involved the result is deafness Mental deterioration begins early and progresses and the bilateral spastic paralysis develops gradually In some cases headache is a prominent symptom and sometimes disc changes are to be found although in typical cases the blindness is not associated with such changes

Pathological Anatomy—The essential pathological condition is a symmetrical demyelinization which usually begins in the occipital lobes spreads forward and is sharply circumscribed Later in the disease the axones become swollen fragmented and destroyed There are proliferation of fibrous astrocytes and

examination confirms these findings with infiltration of the meninges by lymphocytes, plasma and large mononuclear cells with an occasional polymorphonuclear element. There is acute inflammation of the brain and cord showing congestion, small hemorrhages, perivascular cellular infiltration, degeneration of nerve cells and neuronophagia. Local collections of lymphocytes and glial elements are seen independent of the blood vessels.

Diagnosis.—The diagnosis of a meningo-encephalitis is not one of great difficulty provided a lumbar puncture is done. The differentiation of the different types is, however, more difficult and cannot be accomplished with certainty by ordinary clinical methods. However, complement fixation and neutralization tests are valuable aids in reaching a final diagnosis.

Prognosis.—The mortality is about 20 per cent, being higher in the upper decades than in children. If recovery occurs it is usually complete without sequelae.

Treatment.—There is no known specific treatment. Therefore cases are best handled on symptomatic principles. *T. C. M.*

Equine Encephalitis

Horses.—There seems little doubt that horses and mules in this country have suffered from a form of encephalitis for many years, if not decades. It passed under a variety of names until its true nature was revealed by Meyer in 1931 when he demonstrated that a symptom complex was due to a virus and the disease was given its proper designation. In 1933 an epidemic of this disease occurred on the seaboard of New Jersey and Virginia which was demonstrated also to be due to a virus. This virus, however, was immunologically different from the western variety. Hence two forms of equine encephalitis are recognized, namely, the eastern and the western, which are strictly separated by the Appalachian range.

It is now accepted that the virus may be transmitted by many species of mosquitoes, which would account for its spread in local epidemics, but not for its outbreak in distant areas. However, it has been shown that birds (pigeons and pheasants) may acquire the disease and die of it as the virus has been isolated from these birds dying in their natural state. This could account for the distant spread of the disease. A perpetuating vector of the virus may be the tick *Dermacentor andersoni*, which can harbor the virus and pass it on from one generation to another through the ova.

Man.—There is no factual proof that the western variety has affected man. This was first suggested by Meyer, who observed three patients with unclassified human encephalitis who had been in contact with sick horses, but a viral cause was not proved in the patients or the animals.

In 1938 an epidemic of the eastern variety in horses occurred in Massachusetts, with coincident appearance of an unusual number of cases of encephalitis in humans. These latter were proved to be due to the eastern virus, which was isolated from the brains in the fatal cases.

Symptoms and Signs.—These are in general the same as in other encephalitides. The onset in children is usually sudden, with a high fever and frequent convulsions with rapidly progressive coma. In adults the onset may

syndrome or the albumino-cytologic dissociation (in which the patient usually recovered) Other synonyms are acute febrile polyneuritis polyradiculoneuritis infective neuronitis acute benign infectious myelitis polyneuritis with facial diplegia radiculoneuritis with acellular hyperalbuminosis of the spinal fluid (see above)

Definition—It will be noted that most if not all of these synonyms have little or no specific meaning Therefore it is impossible to be concrete as to a definition except that there is a diffuse flaccid paralysis which may differentiate it from acute myelitis mentioned immediately above In fact we are dealing with a potpourri of clinical and pathologic conditions

Etiology—This is a complete mystery It is well not to attempt at present even to suggest a general category Infections of most diverse natures have been suggested as have viruses nutritional factors and chemical agents but they are all speculative

Symptoms and Signs—The onset which may be preceded by a respiratory infection seven to fourteen days before is fairly sudden with fever headaches malaise and weakness to paralysis of the extremities This may progress until the arms legs and intercostal muscles are involved The cranial nerves particularly the seventh may also be affected The paralysis is flaccid and the reflexes are diminished to absent There may be sensory changes with hypo and hyperesthesia to actual acute pain which is most distressing Tingling and formication are common It will be seen that the pattern is that of a lower motor neurone lesion of more or less symmetrical distribution

In a certain number of cases there are also indications of meningeal irritation such as stiffness of the neck and Kernig's sign The spinal fluid is under increased pressure The number of cells usually mononuclear varies considerably from case to case In some with signs of meningeal irritation they may number several hundred per c mm In others they may be within normal limits but with a greatly increased protein content hence the term acellular hyperalbuminosis A leucocytosis is often present

Diagnosis—A specific diagnosis is often difficult It is important to exclude anterior poliomyelitis syphilitic myelitis any or all of myeloencephalitides but even so the remainder present a *conglomerate group* The importance of the diagnosis is more for estimating the possible prognosis than for any specific therapy

Prognosis—The prognosis varies Paralysis of the respiratory muscles will cause death In many cases complete recovery follows beginning with return of function in the parts that were last paralyzed The recovery is consequently a descending progression The convalescence may last for months and sometimes residual weakness and muscular atrophy may remain

Treatment—Absolute rest in bed is necessary and there is usually no other choice because of the paralysis Contracture of the tendo achillis should be prevented by avoiding foot drop When respirations are difficult the patient should be placed in the Drinker respirator If sedatives are necessary morphine should not be given as this further depresses respiration Atropine may prevent the accumulation of secretions in the upper *respiratory passages*

the formation of compound granular corpuscles from microglia Perivascular infiltration with lymphocytes and plasma cells varies considerably in intensity

Prognosis—Death usually results within a period of two to three years and frequently within a few months The disease is progressive but may show slight remissions

Treatment—There is no treatment known

Myelitis

Definition—As the name indicates, this is an inflammatory disease of the spinal cord It is frequently associated with more widespread inflammation and may then become meningomyelitis, encephalomyelitis or meningoencephalomyelitis These terms indicate that the name is a combination of anatomical and pathological description, and that the condition is not specific as to etiology, course or prognosis

Etiology—There is no specific etiology Syphilis is a frequent cause of myelitis and this has been described under the heading of Syphilis of the Nervous System Extension of infection either directly or through the blood stream may also be a cause The term is loosely applied to softening following vascular occlusion or compression of the cord

Symptoms—The onset may be acute or subacute and is sometimes associated with fever The condition may be limited to a few segments, as transverse myelitis or it may involve many segments, as an ascending myelitis The signs of involvement of nervous parenchyma will depend upon the site of the lesion and the structures which are involved In transverse myelitis there is usually a spastic paralysis and some sensory loss up to the level of the lesion Immediately above the lesion there is frequently a zone of hyperesthesia Bladder function is sometimes impaired In the ascending type of myelitis the paralysis may be of the lower motor neurone type from involvement of the anterior horn cells and their axones The cerebrospinal fluid may contain an excess of protein and cells, and in syphilitic cases the Wassermann reaction is usually positive, although in many cases it is negative

Prognosis—The prognosis varies depending upon the cause and the progression of the disease Impairment of respiratory movement and infection of the bladder are serious

Treatment—Symptomatic treatment, the care of the skin and the prevention of urinary infection are the chief indications during the disease Potassium iodide may be used but its value is doubtful If possible the cause should be treated

Acute Flaccid Paralysis

Synonyms—Under this symptomatic title may be grouped a wide variety of so called clinical conditions The confusion is not being clarified by the addition of more synonyms Some aspire to the role of separate conditions because the victim usually recovers others because he usually dies while in others the confusion is enlightened by definite sequelae which makes the diagnosis clear It may be conceded that historically the first synonym was Landry's paralysis (usually fatal) then was enunciated the Guillain Barré

result A form of polioencephalitis is described, in which not only are there lower motor neurone paralyses but there may be upper motor neurone symptoms or cerebellar symptoms in addition The ascending symmetrical type has already been described under the heading of Acute Flaccid Paralysis (see page 1088) The disease may not be confined to motor structures Pain muscle tenderness and stiffness of the back and neck are almost constant features Sometimes sensory impairment may occur from involvement of the spinothalamic tract by the process in the cord The limbs are usually cold and blue

Sequelae—Following the cessation of the acute illness, improvement begins to occur in the involved muscles Usually, however, residual paralyses are left, and these are confined to restricted muscle groups, resulting in paralysis of certain movements such as flexion of the foot or abduction of the arm Since only certain muscles in the limb are affected contractures develop because of the unrestrained action of the antagonists Deformities of the leg are common, such as talipes, and deformities of the spine such as scoliosis and kyphosis also occur Bony growth may be retarded in the involved segment of a limb so that the corresponding segments on the two sides are not only unequal in girth but also in length The residual paralyses are usually very much less in extent than the paralysis that existed during the acute illness, and it is always difficult to determine for some time just how much functional recovery will occur

Pathological Anatomy—There are degenerative changes in the spleen, liver kidneys and lymphoid tissue which becomes hyperplastic The changes in the central nervous system are most marked in the anterior horns of the gray matter There are hyperemia and dilatation of the blood vessels with perivascular hemorrhages and infiltration The infiltration is usually of lymphocytes, but sometimes polymorphonuclear leucocytes are present as well The infiltration extends beyond the perivascular spaces and may involve also the white matter and the meninges The anterior horn cells show all degrees of degeneration to complete destruction and neuronophagia Inflammatory changes may be present in the posterior nerve roots Complete disappearance of motor cells in the anterior horn occurs and fibrous gliosis follows Changes occur in the muscle tissue with atrophy and a relative increase of connective tissue and fat

Prognosis—The prognosis varies in different epidemics and also depends upon the distribution of the lesion Death has been reported in as many as 25 per cent of the cases in certain epidemics This is sometimes due to paralysis of the respiratory center in the medulla and also to bronchopneumonia occurring in cases with paralysis of the intercostal muscles or diaphragm The prognosis as far as sequelae are concerned may be difficult to determine The preservation of faradic excitability in a muscle is of good prognostic significance as it shows that complete degeneration of the nerve supply has not occurred Improvement may be slowly progressive over as long a period as a year In some cases complete recovery takes place and this may even occur where very widespread paralysis existed during the acute illness In other cases residual paralysis contractures and atrophy remain and this disease is a frequent cause of crippling

Acute Anterior Poliomyelitis

Synonyms—Infantile paralysis, Heine Medin's disease

Definition—An acute infectious disease which involves primarily the anterior horn cells and causes a lower motor neurone paralysis

Etiology—The cause of this disease is a filtrable virus which can be transmitted experimentally in animals and clinically in patients The portal of entry has been in dispute Some think it is the nose and nasopharynx with passage along the olfactory nerve More recent opinion holds it is a water borne disease the virus having been found in the stools and in sewage Further it has been shown that water and food may be contaminated by transmission of the virus by flies and mosquitoes

Incidence—Anterior poliomyelitis may occur either sporadically or in epidemic form It occurs in late summer and early autumn and usually disappears with the first frost The incubation period has been variously estimated at from three to fourteen days Males and females are about equally affected Apparently the disease can be transmitted by healthy carriers or by the victims of abortive attacks in which there has been no paralysis Most of the cases occur between the ages of two and four years, beyond that time there is a progressive diminution, although cases quite frequently occur in adult life

Symptoms—The disease is an acute one and paralysis usually occurs within forty eight hours of the onset although in some cases it may be delayed for several days longer The first symptoms are those of general systemic illness, headache malaise congestion of the throat fever, and gastrointestinal symptoms such as anorexia, vomiting and diarrhea These symptoms may last a short time only, and are usually associated with pain on movement of the legs and back The muscles are tender and the neck and back are stiff so that attempts to flex them are painful Kernig's sign may be present Tremors may occur and convulsions are common at the onset in infants At this stage the cerebrospinal fluid is under increased pressure and contains from 50 to 250 cells per c mm The cells are at first both polymorphonuclear leucocytes and lymphocytes but within a few days the former disappear and only a few lymphocytes can be found The protein and globulin are increased but the sugar and chlorides are normal The disease may terminate at any time during the stages just described and paralysis may not occur The paralysis is associated with pain and tenderness of the muscles It may be widespread or local In some cases all four limbs and the trunk may be involved at the same time The distribution however, is usually more limited It is asymmetrical on the two sides and may involve only certain muscle groups in a limb The severity of the paralysis also varies in the different muscle groups The maximum damage is done within the first twenty four hours but sometimes the paralysis is progressive for some days The lower limbs are affected more often than the arms The paralysis is of the lower motor neurone type with atrophy flaccidity and absent tendon jerks Improvement usually begins about the end of the first week and may continue for several weeks Although ordinarily the legs are most affected the brunt of the disease may be borne by the brain stem and cranial nerve paralysis

result A form of polioencephalitis is described, in which not only are there lower motor neurone paralyses but there may be upper motor neurone symptoms or cerebellar symptoms in addition The ascending symmetrical type has already been described under the heading of Acute Flaccid Paralysis (see page 1088) The disease may not be confined to motor structures Pain muscle tenderness and stiffness of the back and neck are almost constant features Sometimes sensory impairment may occur from involvement of the spino thalamic tract by the process in the cord The limbs are usually cold and blue

Sequelae—Following the cessation of the acute illness, improvement begins to occur in the involved muscles Usually, however, residual paralyses are left, and these are confined to restricted muscle groups, resulting in paralysis of certain movements such as flexion of the foot or abduction of the arm Since only certain muscles in the limb are affected contractures develop because of the unrestrained action of the antagonists Deformities of the leg are common, such as talipes, and deformities of the spine, such as scoliosis and kyphosis, also occur Bony growth may be retarded in the involved segment of a limb so that the corresponding segments on the two sides are not only unequal in girth but also in length The residual paralyses are usually very much less in extent than the paralysis that existed during the acute illness and it is always difficult to determine for some time just how much functional recovery will occur

Pathological Anatomy—There are degenerative changes in the spleen, liver kidneys and lymphoid tissue which becomes hyperplastic The changes in the central nervous system are most marked in the anterior horns of the gray matter There are hyperemia and dilatation of the blood vessels with perivascular hemorrhages and infiltration The infiltration is usually of lymphocytes but sometimes polymorphonuclear leucocytes are present as well The infiltration extends beyond the perivascular spaces and may involve also the white matter and the meninges The anterior horn cells show all degrees of degeneration to complete destruction and neuronophagia Inflammatory changes may be present in the posterior nerve roots Complete disappearance of motor cells in the anterior horn occurs and fibrous gliosis follows Changes occur in the muscle tissue with atrophy and a relative increase of connective tissue and fat

Prognosis—The prognosis varies in different epidemics and also depends upon the distribution of the lesion Death has been reported in as many as 25 per cent of the cases in certain epidemics This is sometimes due to paralysis of the respiratory center in the medulla and also to bronchopneumonia occurring in cases with paralysis of the intercostal muscles or diaphragm The prognosis as far as sequelae are concerned, may be difficult to determine The preservation of faradic excitability in a muscle is of good prognostic significance as it shows that complete degeneration of the nerve supply has not occurred Improvement may be slowly progressive over as long a period as a year In some cases complete recovery takes place and this may even occur where very widespread paralysis existed during the acute illness In other cases residual paralysis contractures and atrophy remain and this disease is a frequent cause of crippling

Treatment.—A rigid anti-infectious technic should be observed by all in contact with an acute case and all excreta should be promptly sterilized to prevent further pollution of sewage. During epidemics open air bathing should be prohibited, drinking water boiled, and all uncooked food carefully screened from flies. The administration of convalescent serum has been in use now for some years and the original optimistic reports are somewhat tempered; its value is questionable. Serum from a patient who has had anterior poliomyelitis should be given in the preparalytic stage of the disease, but this stage is extremely difficult and often impossible, to diagnose. From 10 to 25 c.c. of serum, depending on the age of the patient, are given intrathecally by gravity after removal of a slightly larger amount of cerebrospinal fluid. Another amount of serum, sufficient to make a total of 50 c.c., should be given intravenously at the same time. These injections are usually followed by a reaction and fever, and, if fever persists for more than twenty-four hours, another 30 c.c. of serum should be given intravenously or intramuscularly. Hypertonic glucose saline may be given intravenously to reduce edema in severe cases. Hexamine in doses of 10 grains every four hours may be administered but its value is doubtful. When impairment of function of the intercostal muscles and diaphragm makes breathing difficult, the patient should be placed in the Drinker respirator, and atropine may be given to diminish the secretions in the upper respiratory passages. Whereas in the past it was the custom to use splints to prevent contractures, with massage and electric stimulation to maintain and increase the tone of supposedly paretic muscles, it is now held that every means should be used to relax the muscles as they are in a state of tonic contraction rather than paretic. This requires careful handling under expert guidance. It is a revolutionary therapeutic approach introduced by Nurse Kenny. The essential features are keeping the joints in a neutral position, prevention of pressure, use of hot wet packs, all measures to improve the blood supply to the muscles and their re-education under skilled supervision. Swimming in a warm pool is of the greatest value.

Herpes Zoster

Synonym.—Shingles.

Definition.—An acute infection of the posterior root ganglia with signs in the segmental distribution involved.

Etiology.—The cause of this condition is probably a filtrable virus. It may occur with infections elsewhere in the body, particularly lobar pneumonia, malaria and meningococcal meningitis. It may also follow noninfectious lesions of the posterior roots such as injuries or tumors. It has been described in epidemic form and in close relationship to chickenpox. It is most frequent in middle-aged or older adults.

Symptoms.—At the onset of the illness and before the rash appears, there may be fever and pain in the side suggesting pleurisy. On the third or fourth day the rash comes out. It occurs in the segmental distribution of the nerve root involved and it forms papules and vesicles on a hyperemic skin. At first the fluid within the vesicles is clear but it frequently becomes purulent. In the involved area there are burning or shooting pains and hyperalgesia. The lymph nodes draining the area are enlarged. The vesicles may be superficial and heal without scarring or they may be deep and cause disfiguring scars

When the eruption subsides, there may be impairment of sensibility, but at the same time a persistence of the pain. Some of the cranial nerves may be involved in this process and, when the first division of the trigeminal nerve is affected, ulceration of the cornea usually occurs, and this may lead to loss of vision. The affection apparently may spread beyond the posterior root ganglia, and atrophy and weakness have been described in the segmental distribution, presumably from spread of the infection to the anterior horn cells. Signs of meningeal irritation may be present and there may be an increase in lymphocytes in the cerebrospinal fluid. Occasionally other complications occur. Postherpetic neuralgia may persist as a very troublesome sequela. The pain is in the distribution of the involved nerve roots and it is continuous, sharp and burning.

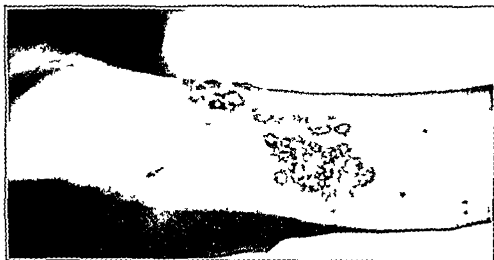


Fig 40 —Herpes zoster in the distribution of the 6th and 8th cervical nerve roots and the 1st thoracic root.

Pathological Anatomy —There are acute hemorrhagic inflammatory changes in the posterior root ganglia and sometimes in the posterior gray horns of the cord, the posterior roots and the peripheral nerves. The condition is rarely bilateral. There is infiltration with mononuclear cells and with a few polymorphonuclear leucocytes arranged as perivascular cuffs. In severe cases the nerve cells show degenerative changes and secondary degeneration is present in the fibers. There are inflammatory changes also in the neighboring leptomeninges and in the skin.

Prognosis —Recovery usually occurs without complications except for some scarring of the skin. When postherpetic neuralgia follows, it may persist for years.

Treatment —The involved area should be covered with powder and a dry dressing. Pituitrin and iodides have been used. Recently diphtheria antitoxin has been described as an effective remedy in this condition. It may be given in a dose of 5 000 units. It may be necessary to repeat this once or twice at intervals of 2 to 3 days. Convalescent serum may be given subcutaneously in doses of 10 c c. When postherpetic neuralgia occurs, alcohol injection or

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paralysis may become complete Other signs of alcoholism may be present, such as alcoholic dementia or Korsakoff's psychosis In Korsakoff's psychosis there is an impairment of memory for recent events, but the patient disregards this and makes up for it by fabrication The prognosis in alcoholic multiple neuritis is usually good although the illness may last for a very long time Death from pneumonia or heart failure may occur during the illness

Lead Neuritis The widespread use of lead in paints water pipes, etc, brings sources of intoxication within the reach of all The neuritis which occurs may be associated with other signs of lead poisoning or with a previous history of lead colic It involves the motor nerves almost entirely and rarely produces sensory changes The paralysis is usually limited to the extensors of the wrists and fingers so that wrist drop is present When the lower extremities are involved, it is chiefly the extensors of the foot which are affected and foot drop occurs Further considerations in regard to lead poisoning are described under the heading of Lead Encephalopathy

Diabetic Polyneuritis This occurs usually in middle aged and older patients and it is possible that circulatory changes are partly responsible for the condition The only evidence of the neuritis may be loss of tendon jerks and severe polyneuritis is exceptional Sensory symptoms are usually prominent and the lower limbs are more affected than the upper There may be considerable pain in the calves Sometimes sense of position is lost, and the term 'diabetic tabes' has been used to describe the condition This term should be discarded

Vitamin Deficiency Peripheral neuritis may occur due to a lack of vitamin B and the disease of beriberi is due to this cause In addition, however, it is likely that certain other types of polyneuritis especially following the use of alcohol, are partly due to a deficiency of this vitamin In beriberi the typical signs of peripheral neuritis are present and in addition, cardiac failure and gastrointestinal symptoms may occur

Acute infective polyneuritis has already been discussed (page 1088)

Pink Disease This disease is also known as erythroedema polyneuritis, trophodermatoneurosis acrodynia and vegetative neurosis (p 794) It affects young children and is characterized by irritability photophobia reddish discoloration and swelling of the hands and feet and the symptoms of polyneuritis Pathologically there is degeneration of myelin and chromatolysis of the anterior horn cells together with a diffuse infiltration with small cells It occurs usually within the first year and a half of life and it has been regarded by some as infective and by others as a deficiency disease The early symptoms are usually those of a mild infection of the upper respiratory tract or of the alimentary canal Afterward the child becomes irritable sleepless and loses his appetite The hands and feet become bluish red slightly swollen and cold There is often an erythematous rash over the body and there is always excessive sweating and desquamation of the hands and feet The rash is extremely irritative trophic disturbances may occur, and analgesia, hypotonia and areflexia may be present

Diphtheritic Neuritis Neuritis may follow diphtheria of the ordinary type and has also been described after diphtheria associated with skin lesions but

section of the posterior root may not relieve the condition and section of the spinothalamic tract, which is conveying the pain fibers from the involved area, may be necessary Deep x ray to the back in the region of the posterior nerve root should be tried before these surgical measures are undertaken

Neuritis

Definition—This term includes those lesions of the peripheral nerves which are due to inflammatory, degenerative or toxic processes

Etiology—A wide variety of etiological agents exists These may be divided into the following groups (1) exogenous poison, such as lead and alcohol, (2) endogenous poisons, such as those of puerperal septicemia and intoxication, (3) metabolic and deficiency disorders, such as diabetes and vitamin deficiency, (4) infections, such as acute infective polyneuritis and diphtheria, (5) other causes, of which there are many

Pathological Anatomy—The pathological changes may be perineural or interstitial, and are usually more marked at the periphery of the fibers There are degeneration of myelin and proliferation of the sheath cells of Schwann some of which become phagocytic Changes in the axones may or may not occur There may be an accumulation of lymphoid elements between the nerve bundles

Symptoms—Neuritis may be local or diffuse and multiple Constitutional symptoms will occur, depending upon the etiological factor The symptoms of the neuritis are pain, impairment of power and impairment of sensation and these symptoms are present in the distribution of the affected nerve or nerves The pain may be sharp, boring, stabbing, and is situated along the course of the nerve and in its distribution Paraesthesiae, such as numbness and formication may be present Frequently the nerve is sensitive along its course so that pressing upon it causes considerable pain The impairment of function of the muscles is of a lower motor neurone type and may be partial or complete Power, reflexes and faradic excitability will be diminished or absent and the muscles will be atrophied Contractures may be brought about through the unhindered action of antagonists All forms of sensibility may be impaired or lost In some cases sensory findings are prominent, while in others they are completely overshadowed by the change in power and reflexes Secondary effects may occur in the distribution of the nerve The skin may be red or edematous its temperature may be raised, and sweating may be excessive Herpetic eruptions and effusion into joints may also occur Polyneuritis or multiple neuritis has a widespread and symmetrical distribution It may be confined to the legs or may involve the arms and even the cranial nerves

Alcoholic Polyneuritis The amount of alcohol necessary to produce this varies considerably in different individuals It is quite likely that the neuritis is not due entirely to the consumption of alcohol, but also to associated metabolic disorders or vitamin deficiency It has been found experimentally that alcohol is capable of producing neurological manifestations much more easily in the presence of vitamin deficiency Sensory disturbances are common in this type of polyneuritis and the muscles become very tender The

except blood in the cerebrospinal fluid, and who develop normally and remain free from sequelae On the other hand, it is likely that a considerable number of patients who develop epilepsy in their teens have suffered birth injuries of which there was never any evidence

Predisposing Factors—The predisposing factors to birth injury are prematurity, prolonged or precipitate labor, disproportion in size between the head and the birth canal the use of instruments and traction Breech presentation is also a predisposing factor because of the traction that is necessary for delivery

Etiology—The mechanical factors that cause the trauma are compression and distortion of the bony structures with resultant damage to the brain and cord stretching or rupture of the spinal cord or of peripheral nerves from traction and compression or laceration of blood vessels and dura with circulatory changes following

Symptoms—The signs and symptoms will depend upon the type of the lesion and its location Damage to the bony structures alone does not give rise to neurological symptoms but such damage is often complicated by involvement of nervous structures These complications are dural hemorrhage from dural tears and tentorial splits subarachnoid hemorrhage from laceration or rupture of veins, and lacerations, contusions and hemorrhages of the brain and cord When the blood is in communication with the subarachnoid space, the cerebrospinal fluid will be bloody

Pathological Anatomy—Lacerations occur of the dural sinuses the tentorium the pia arachnoid the brain and the spinal cord With these there is hemorrhage which may be extradural subdural subarachnoid or within the nervous parenchyma Contusion of the brain and cord with edema and widespread extravasation of blood may also be present Actual rupture of the cord or nerve plexuses may occur The subdural hematomata may organize and also the blood in the subarachnoid space may clot and organize in the arachnoidal villi or adhesions may form about the base of the brain Within the brain and cord softening necrosis and cavity formation or cicatrization may follow contusions and intracerebral hemorrhage

Sequelae—Focal manifestations occurring with birth injury and described below are likely to persist In addition certain end results may follow the pathological conditions described above The obliteration of the arachnoid villi or the adhesions about the base of the brain may cause hydrocephalus (see page 1119) The widespread damage to the cortex may result in mental retardation Convulsive attacks occur frequently either as evidence of focal or general cortical lesions All these sequelae, except the last develop progressively from the time of the injury but the convulsions may not begin until after an interval of many years Retardation of growth of a part of the body may also result with a consequent inequality of the two sides

Prognosis—The prognosis in these cases must always be guarded With birth injuries sufficient to cause symptoms there is always the likelihood of sequelae and when focal signs are present from the start the prognosis is still more unfavorable While much can be done with a child by education

with no faucial lesion Goodall reported, in a large series of cases of diphtheria, that 11 6 per cent showed palsy of some kind Palatal palsy is the most common Then in order come paralysis of accommodation, of the lower limbs, of the upper limbs, of the extraocular muscles, and of the larynx. About 2 per cent develop polyneuritis The symptoms of neuritis ordinarily begin in two or three weeks after the original onset of diphtheria, but they may be delayed for as long as six months The neuritis is manifested chiefly by weakness, but may be associated also with numbness and tingling in the extremities Loss of position and vibration sense occurs quite commonly and these types of sensibility may become involved before those of touch and pain There is no relationship between the severity of the diphtheria and the neuritis Postdiphtheritic neuritis may last a long time, and in some cases the involvement of the nervous system may spread beyond the peripheral nerves and cause a plantar extensor response Lesions have also been reported in the posterior columns of the spinal cord

Progressive Hypertrophic Interstitial Neuritis This rare disease, which is frequently familial and characterized by an interstitial thickening in the peripheral nerves, is described on page 1050

The signs produced by lesions of individual peripheral nerves are described on page 1107 under the heading of Peripheral Nerve Trauma

Treatment—The treatment of peripheral neuritis consists of removing the source of the etiological agent, eliminating it from the body, correcting metabolic disturbances and treating the local condition The involved muscles should be maintained in nutrition by physiotherapeutic measures, and contractures should be prevented or overcome If there is no free hydrochloric acid in the stomach contents, one or two drams of dilute hydrochloric acid may be given well diluted with meals Bed rest is necessary and the general health should be watched A diet rich in vitamin B should be ordered, and if necessary this should be supplemented by administration of the vitamin in other forms Massage, passive movements and galvanic stimulation should be carried out daily as soon as the patient can tolerate them Analgesics and other drugs can be used when the symptoms indicate it

DISEASES DUE TO TRAUMA

Traumatic lesions of the nervous system may be sustained during the process of birth or at any time during life The injury may involve the skull or vertebral column alone or it may cause damage to the nervous structures within, or to the peripheral nerves Apart from the immediate effects of trauma there may be sequelae dating from the time of the accident or not becoming manifest until several years later

Birth Trauma

Definition—Trauma occurring to the child during the process of birth

Incidence—Birth injury is responsible for more than one half of the deaths of viable babies and is the most important single cause of organic nervous disease in children with the exception of anterior poliomyelitis (Crothers) In addition it occurs in many babies who show no signs at birth

The pulse may be slow or rapid The efforts of crying and sucking are feeble There may be rigidity of the neck, retraction of the head, and a bulging nonpulsating fontanelle The pupils are dilated and usually unequal, with the larger pupil on the same side as the subdural bleeding Hyperemia of the optic discs or papilledema and retinal hemorrhages may be seen Convulsions occur and may be generalized or focal Squints, nystagmus hemiplegia and athetosis may be present and persist as sequelae (Fig 408) The cerebrospinal fluid is under increased pressure and contains blood It is often difficult to decide whether certain clinical findings are due to developmental defects or to birth trauma Respiratory difficulty at birth and blood in the cerebrospinal fluid point to the latter cause Developmental defects frequently produce characteristic syndromes, which have been described and the diagnosis is made easy when the signs in the particular case are typical Infantile hemiplegia is usually the result of trauma while infantile diplegia usually results from a developmental defect Microcephaly and microgyria, either unilateral or bilateral, may occur from either cause and sometimes follow a chronic subdural hematoma which prevents full growth of one side of the brain Hematomata of the scalp and depressed skull fractures may follow the use of forceps

Cord Trauma

Injuries to the spinal cord usually result from traction exerted in breech presentations The result may be fracture or fracture dislocation of the vertebral column and stretching laceration or rupture of the spinal cord Meningeal bleeding occurs as described above The damage if high in the cord, may cause death by paralysis of the phrenic nerves In the stage of shock the cord lesion will produce a flaccid paralysis sensory loss and loss of sphincter control As shock wears off and improvement takes place the signs will become less marked and less widespread, and the sequelae will depend on the structures involved

Brachial Plexus Trauma

Brachial plexus palsies result from dislocation of the humerus and traction on the plexus during delivery The distribution of the paralysis depends upon the direction of traction and upon the roots of the plexus which are injured When the entire plexus is involved all the muscles supplied by it are paralyzed and atrophic and the arm is anesthetic When the 5th and 6th cervical roots are involved an upper brachial plexus palsy or Erb s palsy, results This is caused by traction of the head or twisting and depression of the shoulder The muscles paralyzed are the deltoid, biceps brachialis and supinator longus and occasionally some other shoulder girdle muscles The deformity is a typical one (Fig 409) The arm and forearm are adducted and the forearm extended and pronated Supination and flexion of the forearm and abduction and outward rotation of the arm are impossible Atrophy of the involved muscles occurs but usually no sensory loss A lesion of the 8th cervical and 1st dorsal roots causes a lower brachial plexus palsy or Klumpke s palsy This occurs in breech presentations with an after coming arm where great traction is exerted The resulting paralysis is in the muscles supplied by the

training and corrective measures, it is to be borne in mind that structures within the central nervous system, when once completely destroyed, will not regenerate

Treatment—When hemorrhage has occurred, the first consideration of treatment is the removal of the blood In the case of subarachnoid bleeding, this can be done by repeated lumbar punctures, while if the bleeding has been epidural or subdural, the hematoma can be removed by operation Areas of contused or softened brain should be removed so as to prevent the formation of a contracting cicatrix It may be possible to treat the hydrocephalus by the methods described on page 1119 Epilepsy is treated by the removal of the focal cicatrix if one exists Paralysis may require orthopedic measures as well as training and exercises The feasibility of treating mental retardation will depend upon its degree, and the treatment will also consist of training and education Many cases of birth injury are not recognized at birth nor until the child should be sitting up or even crawling or walking The true state of affairs will then become apparent Unfortunately in the past a gloomy outlook was taken by many and the child was considered as incurable Fortunately this attitude is now rapidly disappearing and the spastics themselves are taking a hand in improving the lot of their fellow victims of these birth tragedies A tremendous amount can be done in the way of physical education The principal clue is to make a careful assessment of the probable assets and concentrate on these, but not necessarily to the total neglect of the debits On the other hand concentration on the latter to the neglect of the former is fatal In many cases a great deal can be done to secure for them a useful and happy life with a high morale inherent in the fact of their being wanted

Intracranial Trauma

With intracranial injuries such as those described, the child may be born dead If it is living there is usually respiratory difficulty with cyanosis slow and irregular breathing and death may follow from respiratory failure due to compression of the medulla and paralysis of the respiratory centers there



Fig 408—Birth injury with infantile cerebral diplegia The legs are in marked flexion and the hands especially the left are in a typically athetotic position

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Fig 409 —A child with an Erb s brachial plexus lesion produced during delivery The left forearm is extended and pronated the upper arm cannot be abducted and is rotated inward (From Grinker Neurology Courtesy of Charles C Thomas Publisher Springfield Ill)



Fig 410 —Fracture of the skull in the left parietal region

ulnar nerve and inner head of the median nerve Claw hand is produced by atrophy and paralysis of the small muscles of the hand Sensation may be lost on the inner side of the hand and forearm in the distribution of the ulnar nerve or the 8th cervical and 1st thoracic roots From paralysis of sympathetic fibers a Horner's syndrome results with perhaps also vasodilatation and absence of sweat secretion over the same side of the face The Horner's syndrome is manifested by a small pupil enophthalmos and slight ptosis

Postnatal Trauma

Trauma to the skull and vertebral column can be sustained by direct or indirect injury A blow on top of the head can fracture the cervical spine and a severe fall on the feet when the body is rigid can do the same thing or even fracture the skull From the standpoint of the neurologist a head or back injury becomes of importance when nervous structures are involved and their injury may be out of all proportion to the severity of the trauma suffered by the bones Skull fractures (Fig 410) may be simple comminuted depressed or compound If they are basal they are more likely to be complicated than if they are vertical and in addition, they may be difficult to detect in x ray films Simple fractures require only rest in bed as treatment, whereas if depressions or dislocation of fragments are present they must be relieved by surgical measures If the fracture line communicates with the paranasal sinuses infection of the meninges may further complicate the injury

The vertebral column in the cervical region frequently suffers a fracture dislocation and such an injury is very liable to damage the spinal cord Fractures may occur in other regions of the vertebral column as well but are much less likely to be associated with dislocation The treatment of such injuries to the vertebral column consists of reduction by means of traction and hyper extension and fixation By these measures it is possible to reduce the deformity very quickly but if actual destruction of cord tissue has occurred at the time of the accident this will not regenerate

Intracranial Trauma

At the time of the head injury the following complications may occur concussion contusion or laceration of the brain subarachnoid hemorrhage epidural or subdural hemorrhage with compression of the brain, and intra cerebral hemorrhage In addition there may be sequelae to the trauma in the nature of persistence of focal symptoms posttraumatic headache and dizziness posttraumatic epilepsy and personality changes

Symptoms —*Cerebral Concussion* At the time of the accident the patient is rendered unconscious or consciousness is clouded As he begins to recover he is dull and confused may complain of headache and there may be nausea and vomiting Memory is usually lost for the accident and there may also be a retrograde amnesia or a loss of memory for events preceding the accident The pulse may be slow or rapid and thready and blood pressure may be lowered or slightly increased The pupils may be dilated and if the shock is sufficient tonicity and reflexes may be lost The symptoms of the concussion

may be slight or they may be marked and associated with symptoms of other trauma to the nervous system The recovery from concussion is ordinarily uneventful and rapid

Cerebral Contusion With this there are capillary hemorrhages and edema of the brain The patient is unconscious and may become more deeply so until death occurs, or he may slowly recover from the unconsciousness The intracranial pressure is increased and the optic discs may be hyperemic and congested The blood pressure may increase, and the pulse become slow, and frequent determinations of these are important Headache, vomiting, confusion, and irritability become manifest as consciousness begins to return Focal symptoms may occur as convulsions, cranial nerve palsies or paralysis of a limb or one side of the body

Cerebral Laceration Laceration may occur directly from displaced bony fragments or it may occur because of the force of the injury In the latter case the laceration may be at the site of the violence or directly opposite to it on the other side of the brain or contrecoup There is an actual destruction of tissue with edema and hemorrhages surrounding it The symptoms are like those of contusion, but focal symptoms are much more likely to occur and to persist

Subarachnoid Hemorrhage Frequently with all types of head injury there is bleeding into the subarachnoid space from rupture of veins This condition alone is not serious, although the associated conditions may be The spinal fluid is under increased pressure and contains blood If the bleeding is sufficient in amount there will be some stiffness of the neck and sometimes retraction of the head Repeated lumbar punctures will diminish the intracranial pressure and also remove the blood As the spinal fluid clears, the red blood cells gradually disappear from it and during this process the fluid is yellow

Epidural or Extradural Hemorrhage This occurs from laceration of the middle meningeal artery or one of its branches It may occur with or without a fracture and usually follows a blow in the temporal region Following the initial injury there is unconsciousness from which the patient often recovers After a lucid interval which may last several days, or which may be so short as to escape notice, there is a return to unconsciousness and signs of increasing intracranial pressure begin to appear As the pressure slowly increases, it irritates vasomotor and vagus centers and the blood pressure slowly rises while the pulse gradually becomes slower When the pressure reaches the point where it begins to paralyze these centers the reverse occurs the blood pressure begins to drop and the pulse rate to rise Respirations are at first slow and deep but then become irregular and may be of Cheyne Stokes character In terminal stages they are rapid and shallow With the increasing intracranial pressure unconsciousness becomes deeper and there is often papilledema There may also be focal signs such as inequality in tendon jerks or in tonicity on the two sides paralysis or convulsions of one side of the body or a plantar extensor reflex on one or both sides

Subdural Hemorrhage This occurs from rupture of veins to the sinuses in the dura The bleeding is slow and the signs are vague and may not attract notice until weeks or months have elapsed Not infrequently the con

dition may pass unnoticed for years It may be very difficult to determine the side of the bleeding and for this purpose the only localizing sign may be a homolateral dilated pupil It may be necessary to trephine both sides of the skull to find the hematoma The signs may simulate those of an intracranial tumor with slowly increasing intracranial pressure and vague localizing signs Thus, gradual headache drowsiness, confusion, and papilledema occur The symptoms may fluctuate and hemiparesis, aphasia and sometimes ocular palsies may be present A dilated and fixed pupil on the side of the lesion is common

Intracerebral Hemorrhage Intracerebral hemorrhage occurs in almost all severe head injuries Small petechial hemorrhages in the brain substance and small subpial hemorrhages on the surface may remain discrete or unite to form larger hemorrhagic areas Lacerations and contusions of the brain are associated with surrounding edema and hemorrhage Depending upon the location of these areas focal signs may appear Necrotic foci may also lead to posttraumatic sequelae due to healing by contracting scar tissue

In head injuries the pressure of the cerebrospinal fluid is usually raised though occasionally it may be low Blood is present in most severe cases and the supernatant fluid is yellow or xanthochromic The red blood cells usually disappear in a few days but the xanthochromia may persist for a week or two longer The protein is increased in proportion to the amount of blood in the fluid If the intracranial pressure continues to rise the cerebrospinal fluid pressure will also increase X ray examination is of value both at the time of the injury and later It will show the presence of fractures and plates taken after air injection will show displacements and distortions in the ventricular system from the pressure of dural hematomata and from the pull of contracting scars Leaking of cerebrospinal fluid from the nose or ears is a serious circumstance, as it indicates damage to the intracranial contents and also affords a path for the entrance of infection

Pathological Anatomy —With injuries to the brain hemorrhages occur either from rupture of blood vessels or by diapedesis through their walls These may be small petechial hemorrhages or larger ones caused by the fusion of several or by direct rupture of the vessels Edema occurs around areas of contusion and laceration, and foci of softening and of degeneration and atrophy of the parenchyma are seen Clean cut lacerations heal by a fine glial scar which is not contractile while necrotic areas and contusions made in connection with perforations of the dura heal with a contracting cicatrix containing connective tissue Foreign bodies become encapsulated by mesenchymal and glial tissue The scars which result may sometimes act as bacterial traps and infection may light up from them much later or following operative treatment Old subdural hematomata become covered with a mesothelial membrane

Prognosis —This will depend upon the severity of the injury Uncomplicated cerebral concussion and subarachnoid hemorrhage offer a good prognosis and are rarely fatal Recovery from them is rapid Contusions may prove fatal but ordinarily do not In cases of compression of the brain by epidural and subdural hemorrhages the prognosis is not good and this is

particularly so if treatment is delayed When infection is added to the other conditions, the prognosis is extremely bad The likelihood of the development of sequelae cannot be determined by the severity of the original injury and the prognosis in this respect must always be guarded

Treatment—The first requisite of treatment is rest in bed and even in cases of uncomplicated concussion this should be maintained for three weeks so as to diminish the likelihood of sequelae The room should be darkened and quiet so as to prevent undue irritation The patient should be kept warm and stimulants and analgesics should be given as indicated Blood pressure and pulse rate should be determined at 15 or 30 minute intervals during the acute stage so that increasing intracranial pressure may be detected If the intracranial pressure is higher than normal the head of the bed should be raised, if it is low, the head should be lowered Repeated lumbar punctures will lower the intracranial pressure and also evacuate blood in the subarach
per cent solution) can be given by rectum or hypertonic glucose or sucrose saline
noid space To lower intracranial pressure magnesium sulphate (150 cc of 25
(50 or 100 cc of 50 per cent solution) can be given slowly intravenously Depressed skull fracture and dural bleeding require operation, and softened cerebral tissue should be removed to prevent the formation of a contracting scar

Sequelae—The question of sequelae of head injuries is one of considerable medicolegal importance It is sometimes difficult to determine whether symptoms complained of are real or whether they represent a neurosis or a conscious effort to obtain compensation This is particularly true of posttraumatic headache personality changes and general disability not accompanied by abnormal physical signs

Posttraumatic headache and dizziness form a syndrome which is well recognized at the present time The headache is usually localized to the site of the injury and is a pressing or boring pain Individual attacks of it may be induced by exertion and especially by such movements as stooping over The duration of the attack varies and it is frequently accompanied by dizziness which is also made worse by stooping over The dizziness may be a simple giddiness or an actual feeling of turning or of the movement of objects in the environment Penfield believes that this is due to an abnormality of the leptomeninges following the trauma Encephalography sometimes shows evidence of this by the fact that air escapes from the subarachnoid space to the subdural space If this cannot be determined in films taken immediately after the air injection it may become apparent in films taken one or two days later The treatment of the condition is by the injection of air into the lumbar subarachnoid space or directly into the subdural space at the site of the headache The head is then postured so as to move the air about in this location It is believed that by this means small fine adhesions are broken down Air is used instead of oxygen as it is more slowly absorbed The relief is perhaps brought about through the breaking up of fine leptomeningeal adhesions and reopening of the subarachnoid space

Posttraumatic epilepsy may follow birth injuries or injuries later in life It may begin shortly after the accident or it may be delayed for as long as

ten years or more The attacks are usually focal and the location of the lesion can, in a great many cases, be determined clinically by careful observation and consideration of the pattern of the attack This question has been discussed on page 1006 in the section dealing with the cerebral cortex If a sufficiently accurate description of the attacks cannot be obtained it is possible to induce attacks by hyperpnea or hydration (see page 1153) and to study them Encephalography is of great value in these cases as by means of it focal lesions in the brain may be indicated Such lesions are meningocerebral cicatrices which have followed perforating wounds of the dura and contusion of the brain, and cerebral cicatrices and focal areas of atrophy Foerster and Penfield have shown that scars forming in contused and softened brain tissue are contracting scars that they will exert a pull on the ventricles and so cause distortion and displacement of them The part of the ventricular system which is nearest the scar is characteristically pulled in the direction of the scar and so the ventricular system is asymmetrical on the two sides Areas of focal depression or atrophy of the brain can also be visualized because of the pooling of air about them When posttraumatic epileptic attacks are focal in pattern and when objective evidence of a focal lesion in the brain is present removal of the focus offers a reasonable chance of cure The removal is carried beyond the focal lesion into normal brain, and, as no softened or necrotic tissue is left behind the healing is by means of a thin noncontracting glial proliferation If necessary, medical treatment is continued after the operation

The use and value of electroencephalography are described in the section dealing with epilepsy

Posttraumatic focal symptoms will persist in those cases in which there has been actual destruction of nervous tissue to cause them The central nervous system does not regenerate although peripheral nerves can do so Cranial nerve paralyses are particularly apt to occur and to persist in cases of basal skull fractures The focal symptoms described above may persist if the damage has been complete

Posttraumatic personality changes are particularly difficult to evaluate and to differentiate from neurotic symptoms and from symptoms complained of for the purpose of securing compensation Easy fatigue loss of initiative and ambition irritability impairment of memory and apprehension may be manifest and result in an inability to return to work It is important in evaluating them to inquire carefully into the previous personality of the patient and his mode of reaction to difficult situations Generally it is true that the clearing up of any litigation in connection with the accident is an important part of the treatment In addition psychotherapy and, if necessary the use of sedatives such as bromides and phenobarbital are also employed

Cord Trauma

As stated above damage to the spinal cord is particularly apt to occur with fracture dislocation of the cervical spine Such an injury may follow direct violence or indirect violence such as a severe blow on top of the head It is the type of injury which is often sustained by people diving into very

particularly so if treatment is delayed When infection is added to the other conditions, the prognosis is extremely bad The likelihood of the development of sequelae cannot be determined by the severity of the original injury and the prognosis in this respect must always be guarded

Treatment—The first requisite of treatment is rest in bed and even in cases of uncomplicated concussion this should be maintained for three weeks so as to diminish the likelihood of sequelae The room should be darkened and quiet so as to prevent undue irritation The patient should be kept warm and stimulants and analgesics should be given as indicated Blood pressure and pulse rate should be determined at 15 or 30 minute intervals during the acute stage so that increasing intracranial pressure may be detected If the intracranial pressure is higher than normal the head of the bed should be raised, if it is low the head should be lowered Repeated lumbar punctures will lower the intracranial pressure and also evacuate blood in the subarach per cent solution) can be given by rectum or hypertonic glucose or sucrose saline noid space To lower intracranial pressure magnesium sulphate (150 c c of 25 (50 or 100 c c of 50 per cent solution) can be given slowly intravenously Depressed skull fracture and dural bleeding require operation and softened cerebral tissue should be removed to prevent the formation of a contracting scar

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Posttraumatic epilepsy may follow birth injuries or injuries later in life It may begin shortly after the accident or it may be delayed for as long as

with loss of sphincter control and the signs may increase in severity for a few days It then comes to a standstill for a time after which improvement begins As the lesion is usually chiefly in the grey matter, the residual symptoms are like those of syringomyelia (page 1136)

Meningeal hemorrhage, epidural, subdural or subarachnoid, may occur with trauma to the vertebral column and spinal cord The symptoms vary depending upon the severity, the location, and the amount of compression exerted on the cord Girdle pains or root pains may occur from pressure on posterior nerve roots and will be present in the segmental distribution of the involved roots Compression of the cord will cause a level lesion with signs depending upon the severity of the compression The cerebrospinal fluid will contain blood or blood pigment if the bleeding is in the subarachnoid space Compression of the cord by a dislocation or a hematoma will produce signs of block in the cerebrospinal fluid circulation as described on page 1026

Pathological Anatomy —The meninges may be torn by penetration of dislocated bony fragments and there is often meningeal bleeding The cord substance may be completely or incompletely destroyed with necrosis softening and hemorrhages resulting Connective tissue thickening of the dura and glial and connective tissue scarring of the cord occur Secondary degeneration of the ascending and descending nerve tracts extends up and down the cord

Prognosis —The prognosis depends upon the degree of destruction With complete transection there will be no recovery and the prognosis for life is bad as infection and death eventually occur With incomplete transection residual signs will remain depending upon the structures destroyed Paraplegia sensory loss and bladder disturbance also offer a poor prognosis The signs of hematomyelia tend to improve and may leave only slight sequelae

Treatment —In cases of dislocation of the vertebral column the treatment consists of reduction by traction and fixation In dislocations of the thoracic and lumbar vertebrae hyperextension aids in the reduction Bone grafting may be necessary in some cases to secure the fixation In complete transection no other immediate treatment will help but in incomplete lesions operation may be indicated for the removal of foreign bodies Care of the skin and of the bladder is necessary to prevent trophic disturbances and infections Orthopedic treatment may be necessary in the treatment of the original injury and of sequelae

Sequelae —*Focal signs due to actual destruction of the cord will persist* Sometimes Kummel s disease may occur months after an injury to the back which may not be severe In this condition there is softening of the bone and a spondylitis with ankylosis Intercostal pain pain in the back, and slight weakness in the legs may occur because of compression of nervous structures

Peripheral Nerve Trauma

Symptoms —Trauma to a peripheral nerve causes cessation of its function and produces motor sensory vasomotor and trophic disturbances in the area which it supplies The weakness or paralysis is of the lower motor neurone

shallow water. In other regions of the vertebral column fracture dislocations may follow injuries which forcibly double up the individual or hyperflex the spine. Dislocations are less likely to occur with fractures of the thoracic or lumbar spine owing to the fact that they are more fixed and heavily muscled than the cervical region. Contusion of the cord may occur without gross injury to the vertebral column.

Symptoms.—If destruction of the cord is complete, or if a great deal of shock accompanies the original trauma to the cord, the signs will be those of transection of the cord. All power, sensation, tonicity, and reflexes will be lost below the level of the lesion and there will be retention of urine and feces. If the transection has been complete, these signs will begin to change in about ten days or two weeks, and functions of the isolated cord will begin to return (page 1018). The establishment of these functions will take another two to three weeks. Tonus returns and stimulation of the soles of the feet or the skin of the legs causes a triple flexion mass reflex. At the same time automatic emptying of the bladder, and perhaps of the bowels, begins to be established, and the patient will void at intervals without being aware of it. Infection of the bladder eventually develops and this ascends in the urinary tract and later causes a septicemia from which death results. If the transection has not been complete, the signs of shock will recede quickly and leave only the manifestations of the actual damage that has occurred in the cord. Thus pyramidal tract involvement may result in a paraplegia, sensory tract involvement in sensory loss, and the signs will be present from the level of the injury downward over the remainder of the body. With these impairments there is often disturbance of bladder function. The paralysis and sensory loss may be complete or incomplete depending upon the degree of damage and improvement may continue over a long period of time. If the lesion is high in the cervical cord, death usually results from involvement of the phrenic nerves and respiratory difficulty. If the level is at the 6th cervical segment, the adductors of the arm and extensors of the forearm are paralyzed so the arms become abducted and the forearms flexed. A lesion of the 7th cervical segment causes adduction of the arms and flexion of the forearms because of paralysis of the deltoid and triceps muscles. Involvement of the 8th cervical and 1st thoracic level causes a Horner's syndrome (see page 1017). Paralytic symptoms following cauda equina lesions are lower motor neurone in type. Their distribution and also that of the sensory loss will depend upon the roots involved. Usually bladder function is impaired and sexual power lost.

Hematomyelia or bleeding into the spinal cord may be caused by trauma or vascular or blood diseases. The trauma may be a direct one or an indirect one, and such bleeding may follow the general concussion of explosions. At the time of the injury the vertebral column may be injured or it may not and the hematomyelia may be associated with contusion of the cord or with meningeal hemorrhage. As with hemorrhage elsewhere in the nervous system the onset of symptoms is sudden. The artery involved is usually the anterior spinal artery or one of its branches. At the onset there is usually a paraplegia

Division of the musculocutaneous nerve causes marked weakness of flexion of the elbow joint, although the supinator longus may partly compensate for this Sensation is impaired on the radial border of the forearm, as low as the carpometacarpal joint of the thumb

With paralysis of the ulnar nerve the hands deflect to the radial side, adduction of the thumb is impossible, the first phalanges cannot be flexed, and the others cannot be extended *This may lead to a typical deformity called the "clawhand" in which the fourth and fifth fingers are extended at the metacarpophalangeal joint and flexed at the interphalangeal joints* The loss of sensation is over the little finger and the adjacent half of the fourth finger Sometimes this anesthesia extends to half of the third finger over the back, and to the ulnar side of the hand

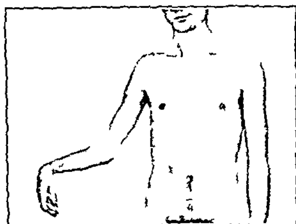


Fig 411 —Wrist drop on the right side from a paralysis of the extensor muscles in a musculospiral nerve lesion

The median nerve is rarely affected alone The *signs of involvement are* inability to pronate the forearm beyond the midposition, deviation of the hand to the ulnar side when the wrist is flexed against resistance, and the thumb cannot be opposed to the tips of the fingers nor abducted when at right angles to the palm The terminal phalanx of the thumb and the phalanges of the index finger cannot be flexed There is weakness of flexion of the phalanges of the remaining fingers but not complete paralysis because the ulnar half of the flexor digitorum profundus is supplied by the ulnar nerve Sensation *is lost on the radial side of the palm* and the front of the thumb the first two fingers and half of the third finger *and the dorsal surfaces of the same* three fingers

In paralysis of the peroneal nerve there is foot drop and the foot cannot be dorsiflexed Because of this when the patient walks he must raise the leg *high from the ground* in order to clear it and this produces a characteristic gait The loss of *sensation is over the outer half of the front of the leg* and on the dorsum of the foot

Treatment.—The treatment of these conditions consists of *maintenance of* muscle nutrition prevention of contractures, removal of pressure upon the

type Sensation is lost in the area of skin supplied and sometimes sympathetic phenomena occur The trauma may be pressure, crushing, laceration or stretching It may be mild, and followed by rapid recovery, or there may be complete section of the nerve with degenerative and regenerative processes going on within it (page 1020) While these are progressing simultaneous changes are going on in the muscles Peripheral nerves to the arms and legs arise from plexuses which are formed by many nerve roots In the plexus there is a rearrangement so that peripheral nerve distribution and segmental distribution are not identical Consequently in lower motor neurone lesions and the sensory impairment associated with them, it must be determined whether the distribution is that of a peripheral nerve or of a nerve root The distribution of a peripheral nerve may vary a little because fibers from one nerve may extend into the territory of another For the innervation of muscles and the cutaneous distribution of peripheral nerves a textbook on anatomy should be consulted and it will be necessary to do so when the individual cases are being studied A nerve may be involved in its distal portion and muscles supplied from more proximal levels will be intact The symptoms which occur with lesions of the nerves most commonly involved are described below

Lesions of the brachial plexus have been described under the heading of Birth Injuries on page 1096

The posterior thoracic nerve is usually injured by a blow or prolonged pressure upon the shoulder This nerve supplies the serratus magnus muscle which fixes the scapula to the chest when forward pressure is exerted with the upper limb and assists in elevating the arm above the head by rotating the scapula When it is paralyzed there is no deformity while the arm is at rest but if the patient pushes the arm forward against resistance the scapula becomes markedly winged In addition he is unable to raise the limb above the head in front of him

The circumflex nerve which supplies the deltoid and teres minor muscles may be injured by lesions in the neck of the humerus The results are wasting and paralysis of the deltoid muscle and marked weakness of abduction of the arm In addition anesthesia and analgesia occur in an oval area extending from the acromial process halfway down the other aspect of the arm

The musculospiral nerve may be interrupted in the axilla and will then cause paralysis of extension of the elbow joint and paralysis of the supinator longus which will not contract when the forearm is flexed while in a position between pronation and supination Paralysis of the supinator brevis leads to loss of supination There is paralysis of the extensors of the wrist and fingers with a consequent wrist drop and finger drop (Fig 411) Flexion of the fingers in gripping an object is also impaired because of absence of the synergic extension of the wrist which should occur with this movement When the nerve is injured in the lower third of the arm as most frequently happens the triceps muscle will escape and the wrist drop and finger drop will be the chief disability

The focal symptoms which occur in uncomplicated subarachnoid hemorrhage are usually due to cranial nerve involvement at the base of the brain Associated with the subarachnoid hemorrhage, there may be hemorrhages into the retina, and sometimes slight papilledema

General Symptomatology —Symptoms of general systemic disease, and of predisposing causes to vascular lesions within the brain, will be present when these exist Inflammation about the ears or face which may lead to sinus thrombosis within the cranial cavity will present characteristic signs Cardiovascular renal disease which is so often associated with cerebral complications and such blood diseases as purpura hemorrhagica and polycythemia will manifest the symptomatology which has been described elsewhere Traumatic lesions and neoplasms of the brain are described under their own headings and will present their own signs It is important, therefore, in vascular diseases of the nervous system to search throughout the entire body for predisposing or causative factors

As indicated above aneurysms may be congenital or acquired They may be arterial or arteriovenous, and they may or may not cause symptoms until hemorrhage occurs from them When that happens the signs are those of subarachnoid hemorrhage Symptoms occurring before rupture of the aneurysm will depend upon its size and location, and very frequently it is too small to make itself manifest Sometimes headache tinnitus, and bruits occur The bruits coincide with systole cause a throbbing rushing sensation and may be audible on auscultation of the head These bruits occur particularly with arteriovenous aneurysms Unless the aneurysm is very large, there will be no signs of increased intracranial pressure Focal manifestations are usually those of cranial nerve involvement and with them there may be homolateral exophthalmos X ray examination may show some calcification in the wall of the aneurysm or erosion of the adjacent bone from pressure In addition the injection of thorotrast may outline the dilatation (Fig 413)

Cerebral hemorrhage thrombosis and embolism may be impossible to differentiate from one another by clinical examination Hemorrhage occurring as a sequela to trauma and located in the dural or subarachnoid spaces or in the brain is described under the heading of Trauma of the Nervous System In subarachnoid hemorrhage the symptoms are those due to meningeal irritation and to focal involvement as described above Crossed hemiplegia and bilateral pyramidal tract involvement may also occur On lumbar puncture a bloody xanthochromic spinal fluid is obtained at the time of or after the hemorrhage Intracerebral embolism thrombosis and hemorrhage (Fig 414) are of sudden onset Sometimes vague premonitory signs may have been present before the hemorrhage or other complication occurred Unconsciousness usually occurs at the onset although in cases of thrombosis this may not be so In thrombosis also the signs may take from 24 to 48 hours to develop whereas in hemorrhage and embolism they occur immediately These conditions occur chiefly in middle age and are associated usually with disease of the cardiovascular system At the onset symptoms may be widespread because

In addition to hemorrhages, trauma may also cause arteriovenous aneurysms. Inflammatory lesions such as periarteritis nodosa, syphilis and others may cause aneurysms, thrombosis or embolus of the vessels Tumors of the blood vessels, such as hemangiomata and hemangioblastomata, are also responsible for vascular lesions Arteriosclerosis may be associated with cardiac and renal disease and may produce symptoms either of a diffuse character or focal manifestations following thrombosis or hemorrhage In inflammatory diseases of the heart vegetations may become detached and form emboli in the brain In purpura hemorrhagica and in polycythemia vera vascular changes may be produced in the brain in the former disease hemorrhage may occur and in the latter thrombosis Cerebral hemorrhage may be associated with cerebral tumor and occasionally the first evidence of the tumor may be caused by the hemorrhage

Pathological Anatomy—The pathological mechanism of the production of lesions due to the causes named above, is described in Chapter VII Cessation of circulation may occur during asystole in Stokes Adams disease Vascular spasm within the brain is associated with fleeting clinical manifestations and may produce changes in the ganglion cells within the involved area Hemorrhage may occur with or without rupture of vessel walls and may take place into the epidural subdural or subarachnoid spaces or into the brain substance itself Hemorrhage thrombosis and embolus of cerebral vessels are accompanied by necrosis and softening of the brain tissue supplied by the vessels Disturbances in innervation may produce prolonged vasoconstriction such as occurs in Raynaud s disease

Symptoms—The onset of symptoms in cerebral vascular disease is usually sudden and the focal signs depend upon the location of the lesion In chronic progressive diseases of vessels however such as arteriosclerosis and aneurysms slowly progressive symptoms may be found When hemorrhage, thrombosis or embolus becomes associated with these diseases the onset of the symptoms which they produce is sudden The symptomatology of epidural and subdural hemorrhage is discussed under the heading of Trauma of the Nervous System

When subarachnoid hemorrhage occurs, the blood acts as an irritant to the meninges and the signs are consequently those of a meningitis with or without focal manifestations The onset is sudden the neck is stiff the head may be retracted and there may be a positive Kernig's sign Lumbar puncture yields a bloody spinal fluid if done early As the blood begins to disappear from the spinal fluid the supernatant fluid becomes yellow in color and this xanthochromia persists for some time after all the red blood cells have disappeared Subarachnoid hemorrhage may occur in young adults usually from rupture of a congenital aneurysm and it may also occur later in life from the same cause or from any lesion which will produce bleeding into the subarachnoid space Intracerebral hemorrhages which break into the ventricles or into the subarachnoid space will also cause the appearance of blood in the spinal fluid

of reaction and edema about the area primarily involved, but the neighborhood symptoms may rapidly clear and leave only the focal symptoms due to direct involvement

The degree of cerebral arteriosclerosis that may exist need not necessarily be in proportion to that manifested elsewhere in the body The neurological manifestations that are brought about are due to chronic progressive diminution in circulation and also to sudden vascular lesions usually of a thrombotic nature The symptoms of cerebral thrombosis have been described above The progressive ischemia may produce symptoms so slowly that they receive no special notice These are progressive reduction in intellectual capacity, an impairment of memory particularly for recent events and some emotional instability The memory for remote events is retained, and the patients spend much of their time in reminiscences about the past There are likely to be personality changes also with the individual becoming self centered and disinclined to change his mode of life Depression and delusions sometimes occur The intellectual impairment may progress to the point of dementia when the patient becomes confused, disoriented and deteriorated Tremor is present frequently in cerebral arteriosclerosis and paralysis agitans also occurs

Focal Symptomatology—The principles of the anatomical diagnosis of nervous diseases have already been discussed in the section with that title, and some of the characteristic syndromes which occur have been described Vascular disease and its acute complications hemorrhage, thrombosis and embolism, may occur any place in the central nervous system and so the focal signs may vary considerably When a single vascular lesion will produce signs of involvement of different functional pathways, it must be located where those pathways meet in such a manner that their destruction will produce the signs manifested This is well exemplified in the crossed paralyses which have already been described When vascular lesions are diffuse or multiple the various functional pathways may be involved separately and in different locations The most common location of vascular lesions of middle age is in the lenticulo striate artery which supplies the internal capsule It has already been described how the motor pathways descend in the anterior part of this capsule and how sensory fibers ascend behind them In addition the visual or optic radiations to the occipital lobes pass through the internal capsule posterior to the sensory fibers A lesion in this location therefore depending upon its size may cause a hemiplegia on the opposite side of the body a hemianesthesia on the opposite side of the body a hemianopsia to the opposite side of the body or any combination of these three Very frequently all three conditions obtain and they will be associated with aphasia if the lesion is in the dominant hemisphere At the onset of a sudden hemiplegia tonicity may be diminished and tendon reflexes absent but ordinarily within a few days these signs change to those typical of pyramidal tract involvement At the onset of cerebral hemorrhage the coma may be so deep and shock so pronounced that diagnosis of the condition is difficult In such cases the odor of the breath should be noted and urine and blood examined so that if uremia or diabetic coma is present, it may be adequately treated

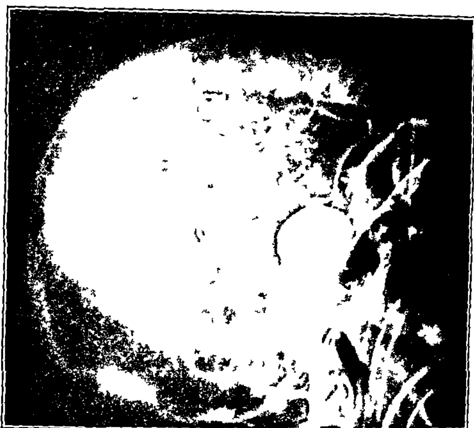


Fig 413 — Aneurysm of the intracranial portion of the right internal carotid artery x rayed during the injection of thorotrast In this case there was a smaller aneurysm on the left side also (compare with Fig 400) (Courtesy of Dr Wilder Penfield)

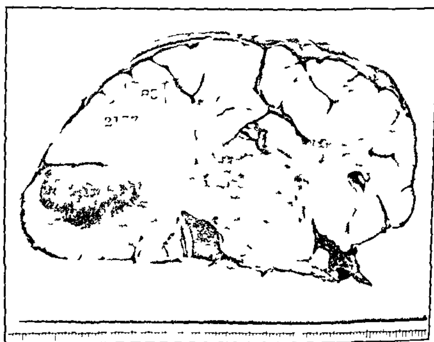


Fig 414 A l rg b l rrhag

extend into the jugular vein in which case pressure on the neck will cause tenderness and the vein may even be felt as a hard cord If infection involves the meninges there will be an increase of cells in the cerebrospinal fluid and these will be of the polymorphonuclear variety

Pathological Anatomy —The pathological findings are those of thrombosis There will be some organization and canalization of the thrombus Hemorrhagic softenings may occur in the superficial parts of the brain

Prognosis —The prognosis is grave and the mortality rate is high

Treatment —The source of infection must be treated and, in lateral sinus thrombosis surgical intervention should be carried out

Paralysis Agitans

Synonym —Parkinson s disease, or the Parkinsonian syndrome

Definition.— A chronic disease characterized by rigidity tremor slowness of movement and the impairment of certain so called automatic movements

Etiology —The condition is a symptom complex due to lesions involving the corpus striatum or the substantia nigra and consequently it may be caused by various etiological agents In young patients it is usually a sequela of epidemic encephalitis whereas beyond middle age it is usually associated with arteriosclerosis

Symptoms —The disease may be bilateral or unilateral Its onset is gradual and it frequently begins on the one side and then extends to the other While the disease is named the shaking palsy " in some cases tremor may be absent The tremor may begin in one hand and then spread to involve the other both legs and even the head It is a slow tremor which is made worse by emotion and usually stops during voluntary movement but begins again as soon as the movement ceases It has been called a pill rolling tremor because of the position of the thumb and fingers during it The rigidity involves all the muscles of the affected part It may become extreme It is frequently of the cogwheel variety which is an intermittent relaxation and contraction as the muscle is passively moved The generalized rigidity and impairment of movement cause a characteristic attitude on the part of the patient The face is smooth and masklike the eyes blink rarely and the expression does not change As the attitude (Fig 415) of the patient is usually one of flexion the eyebrows are elevated as he looks forward The head and back are bowed forward and the arms are semiflexed at the elbows Movements are slow and are particularly difficult to start Thus a seated patient may take half a minute or more before he can initiate the movements necessary to stand up Writing becomes impaired because of the tremor and rigidity and it is irregular uneven and small Movements are carried out en bloc so that in turning all segments of the body turn at the same time and slowly and with deliberation In walking the patient takes short slow dragging steps and his body seems to be in advance of his feet so that he has difficulty sometimes in stopping This is called propulsion and festination In walking also the arms do not swing at the sides but hang motionless and rigid Propulsion

Prognosis—The prognosis in these vascular lesions depends upon the site of involvement and the extent of involvement Deep coma at the onset, and the persistence or increase of coma are grave signs The question as to how many residual signs will remain cannot be answered for some weeks Complete recovery may be made or focal symptoms may persist, usually those of hemiplegia or aphasia Partial recovery may occur so that the patient is able to walk around and carry on a fairly active life, even though almost complete uselessness of the arm may persist

Treatment—It is probable that rest in bed, and nothing more, is as effective as any more active measures The general health should be watched The patient should be changed in position from time to time, so as to prevent congestion of the lungs The bowels should be kept free, and catheterization may be necessary Diminishing intracranial pressure by lumbar punctures, bleeding, and the use of magnesium sulphate solutions by rectum have all been recommended, but their value is doubtful If the patient is unconscious or if sensation is impaired great care must be taken in the use of hot water bottles, which may readily burn the skin When the acute illness has subsided, passive movements, massage, and reeducation may help The likelihood of further attacks must be kept in mind

Venous Sinus Thrombosis

Etiology—Thrombosis of the intracranial venous sinuses usually results from the extension of infection to the sinuses from neighboring structures such as the ears, nasal accessory sinuses or face In addition it probably occurs rarely in marasmus and cachectic states in infancy and in old age

Symptoms—In addition to the symptoms of the disease which is responsible for the thrombosis there are symptoms of septicemia and of defective venous drainage from the area of scalp adjacent to the sinus The temperature is increased and irregular The pulse is rapid and there may be rigors Extension to the leptomeninges may cause signs of meningitis, and pulmonary embolism will cause pyemic abscesses in the lungs There is mental dullness which may progress to delirium and vomiting and convulsions may occur

In thrombosis of the cavernous sinus, there is edema of the optic discs orbits conjunctiva and face in the region of the eye As the third, fourth and sixth cranial nerves lie in the wall of the sinus there may be ophthalmoplegia either partial or complete Exophthalmos occurs because of the congestion and edema of the orbital structures Pain is severe and felt in the region of the eye and forehead

When thrombosis of the superior longitudinal sinus occurs there is a rise in intracranial pressure with headache vomiting and papilledema occurring There is usually retraction of the head and there are sometimes convulsions squint, and bilateral pyramidal tract signs in the legs

In thrombosis of the lateral sinus which usually follows infection of the mastoid, there is pain in the ear and swelling and edema of the scalp in that region Delirium and vomiting occur and sometimes slight pyramidal tract signs will be manifest on the opposite side of the body The thrombosis may

Prognosis —The course of the disease is slowly progressive and it may last for years Of itself it does not interfere with life

Treatment —Some improvement may follow the administration of hyoscine belladonna or stramonium Hyoscine hydrobromate may be given in doses of gr 1/150 or 1/100 three times a day If salivation is a prominent symptom tincture of belladonna minims 5 to 15, may be added In some cases it is found that tincture of stramonium is more beneficial This is started in doses of 10 minims three times a day and gradually increased until 40 to 60 minims are taken at each dose Benzedrine sulfate in doses of about 10 mg morning and noon helps many cases also

Raynaud's Disease

Definition —Impairment of the circulation in the fingers and toes, which is usually symmetrical and accompanied by phasic color changes (Fig 416)

The condition is due to vasoconstriction of the smaller arteries Acrocyanosis in which the extremities are constantly blue and abnormally cold is a closely allied condition These have been discussed in detail under Diseases of the Blood Vessels (Chapter VII) Patients with Raynaud s disease may develop symptoms of vascular spasm in other parts of the body especially in the nervous system and this may lead to transitory symptoms such as amblyopia, migraine epilepsy aphasia, hemiplegia etc

Hydrocephalus

Hydrocephalus is an increased accumulation of cerebrospinal fluid within the cranial cavity It may result passively from atrophy of the brain or actively from an increased formation or deficient absorption, of cerebrospinal fluid This fluid is formed within the ventricles leaves them by way of the foramen of Magendie and the foramina of Luschka circulates in the subarachnoid space and is absorbed primarily from the arachnoidal villi into the dural sinuses There are two types of hydrocephalus an obstructive type and a communicating type In the obstructive type fluid within the ventricles cannot get into the subarachnoid space because of an obstruction to its circulation In the communicating type there is free communication between the ventricles and the subarachnoid space but there is a disturbance in the formation or the absorption of the fluid or an obstruction to the circulation within the subarachnoid space so that the absorbing mechanism cannot be reached

It is possible that, if the pressure of blood in the veins draining the chorioid plexus is increased excessive formation of cerebrospinal fluid takes place but if this is so it must be a rare occurrence This mechanism has been used in part to explain the hydrocephalus that occurs in subtentorial tumors It has been stated that displacement of the tentorium upward compresses the vein of Galen against the splenium of the corpus callosum, and so causes congestion in the chorioid plexuses But tumors in the same location also interfere with the drainage of the ventricles and this is the more likely mechanism

is also manifest when the patient is given a gentle push forward and has great difficulty in bringing himself to a standstill On being pushed backward he may manifest retropulsion and may show lateropulsion as well If the patient is seated in a chair, which is suddenly tilted from behind he will not throw up his legs in an effort to preserve his balance, as a normal individual would do The voice becomes hesitant, monotonous and shrill, and there is often an initial retardation before speech can be started In the type of paralysis agitans which follows encephalitis, there is usually excessive secretion of sebaceous material over the face and excessive saliva in the mouth In addition, in this type, other sequelae of epidemic encephalitis may be present, especially oculogyric crises and sometimes dystonic movements



Fig 415 —Paralysis agitans The arms and wrists are semiflexed the body stiff and flexed forward (From Grinker Neurology Courtesy of Charles C Thomas Publisher Springfield Ill)

In young people who show the Parkinsonian syndrome after encephalitis, and who have the greatest difficulty in carrying out ordinary movements, there may be surprising agility when movements requiring greater volition are performed Thus although he has great difficulty in walking, the patient may be able to run or swim well In the same way, a patient who is almost immobile may display great agility in catching a ball which is thrown at him without warning

Pathological Anatomy —There is degeneration within the striate body and the globus pallidus with atrophy and diminution in the number of large motor cells in this region Large areas of degeneration may form lacunae which are macroscopically visible Similar degeneration and atrophy of cells occur in the substantia nigra

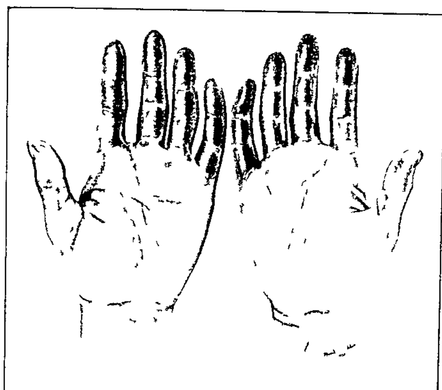
of the production of hydrocephalus in these cases Obstruction to the flow of cerebrospinal fluid may occur at any point, but its most frequent locations are in the aqueduct of Sylvius in the subarachnoid space at the base of the brain or in the region of the Sylvian fissures In the case of block of the aqueduct, *obstructive hydrocephalus results whereas, when the lesion occurs* at the level of the Sylvian fissure, free communication between the ventricles and the subarachnoid space exists and the hydrocephalus is of the communicating type Obstruction may also occur at the foramen of Munro in which case the hydrocephalus will involve only one lateral ventricle



Fig 417 —Hydrocephalus in a child The head is enlarged and full in contour and the frontal bones are bulging and prominent.

The obstruction may be due to congenital atresia of the aqueduct of Sylvius to adhesions following inflammatory lesions or to tumor growth Congenital atresia of the aqueduct of Sylvius or of the foramina in the brain stem is sometimes associated with other congenital abnormalities such as clubfoot spina bifida or harelip Defect in absorption may follow obstruction of the arachnoidal villi and their obliteration by the extension of inflammatory products in cases of leptomeningitis or of extravasated blood in cases of subarachnoid hemorrhage The inflammatory product or the extravasated blood may then become organized leading to a permanent defect

Symptoms—Hydrocephalus acquired in early infancy is associated with enlargement of the head which may become extreme (Fig 417) The sutures are separated and the fontanelle is enlarged and there is marked congestion of



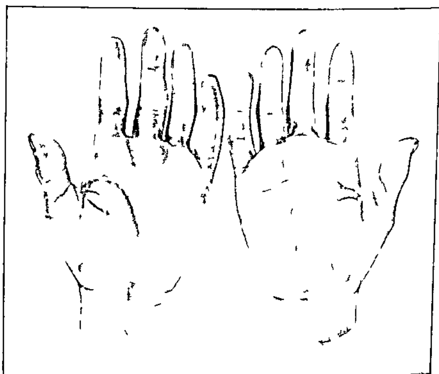


Fig 416—A drawing of the phasic color changes in Raynaud disease Above intense cyanosis of fingers fading in palm and absent above the wrist Below pallid asphyxia of finger tips (From White The Autonomic Nervous System The Macmillan Company New York 1935)

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Symptoms.—Hydrocephalus acquired in early infancy is associated with enlargement of the head which may become extreme (Fig. 417). The sutures are separated and the fontanelle is enlarged and there is marked congestion of

the veins of the scalp. In extreme cases the head may be translucent and may yield a thrill and a murmur. Ordinarily the frontal region bulges forward and the eyes may be pressed forward and downward. Because the skull can expand, signs of increased intracranial pressure are not conspicuous but they may be present. Convulsions commonly occur. Papilledema or optic atrophy, or both, may be present and vision may be lost. Frequently strabismus and nystagmus are present. Usually there are weakness and incoordination of the limbs more marked in the legs than in the arms. Spasticity with increased reflexes, or absent reflexes, may occur. The plantar responses are usually extensor. The mental state varies and there is usually little or no disturbance in sensibility.

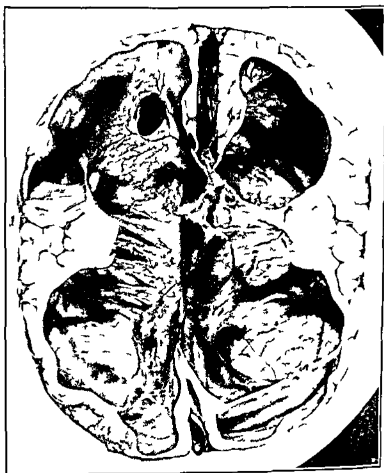


Fig. 418.—Tremendous internal hydrocephalus with distortion and thinning of the brain and dilation of the ventricles.

When hydrocephalus is acquired in later life, signs of increased intracranial pressure are conspicuous. Headache, vomiting and papilledema occur and optic atrophy and blindness follow. Clouding of consciousness and intellectual deterioration may be present in advanced cases. Before the age of eighteen years there may be slight separation of the sutures and a cracked pot note, but after the age of eighteen enlargement of the head does not occur. Frequently, especially in children, there is venous congestion of the scalp

Cranial nerve paralyses, especially of the sixth nerve exophthalmos clumsiness and incoordination and changes in the reflexes may be present.

X ray examination may show separation of the sutures convolutional markings thinning of the bones erosion of the clinoid processes and deepening of the sella turcica If the hydrocephalus is of the communicating type roentgenograms taken after the injection of air into the lumbar subarachnoid space will show the presence of dilated ventricles If however the hydrocephalus is obstructive such air will not enter the ventricles and the site of the obstruction may be apparent In obstructive hydrocephalus air injected directly into the ventricles will show dilated ventricles often to an extreme degree so that only a thin layer of cerebral tissue remains If dye is injected into the ventricles and can later be obtained from the subarachnoid space the hydrocephalus is apparently of the communicating type If on the other hand the dye cannot be recovered the hydrocephalus is obviously obstructive in nature Furthermore in obstructive hydrocephalus the pressure of cerebrospinal fluid in the ventricles differs from that in the subarachnoid space in the lumbar region, whereas in communicating hydrocephalus the pressure is the same in the two locations and is raised

In addition to the signs of the hydrocephalus there will be signs also of the lesion which is causing it particularly if this is a cerebellar or brain stem tumor

Pathological Anatomy —There are dilatation of the ventricles and thinning of the hemispheres (Fig. 418) with some atrophy of the cortical ganglion cells The cause of the obstruction presents its own pathology

Prognosis —Most cases of congenital hydrocephalus prove fatal within the first few years of life The prognosis in acquired cases depends upon the cause and how amenable it is to treatment

Treatment —This consists of removing the cause of the hydrocephalus or destroying the choroid plexus by cautery or by removal or of providing a new outlet which will allow spinal fluid to reach the absorbing surfaces of the arachnoidal villi To bring about the last it may be possible to dilate the aqueduct of Sylvius or to make a new foramen of Magendie or to puncture *the corpus callosum or amputate the anterior pole of the temporal lobe* To diminish the increased intracranial pressure before operation lumbar puncture can be carried out in cases of communicating hydrocephalus fluids can be restricted and hypertonic glucose saline solution can be given in either type of hydrocephalus Treatment however is unsatisfactory

TUMORS OF THE NERVOUS SYSTEM

Tumors of the nervous system may be primary or secondary (metastatic) The term is used here to include the infective granulomata due to tuberculosis and syphilis The tumors may be located in the bones of the skull or vertebral column in the meninges in the blood vessels or in the nervous tissues of brain cord or peripheral nerves They may be benign or malignant Primary tumors of the intracranial and intravertebral structures do not metastasize elsewhere in the body but in some cases they may metastasize from one area of

the veins of the scalp. In extreme cases the head may be translucent and may yield a thrill and a murmur. Ordinarily the frontal region bulges forward and the eyes may be pressed forward and downward. Because the skull can expand, signs of increased intracranial pressure are not conspicuous but they may be present. Convulsions commonly occur. Papilledema or optic atrophy, or both, may be present and vision may be lost. Frequently strabismus and nystagmus are present. Usually there are weakness and incoordination of the limbs more marked in the legs than in the arms. Spasticity with increased reflexes, or absent reflexes, may occur. The plantar responses are usually extensor. The mental state varies and there is usually little or no disturbance in sensibility.

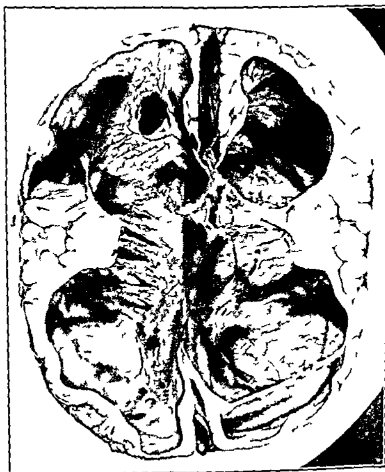


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quently leads to paralysis of one or both sixth nerves with consequent paralysis of external rotation of the eye or eyes and convergent strabismus (Fig 419)

Convulsions beginning in adult life must be regarded as due to structural change in the central nervous system unless proved otherwise These convulsions may be general but are usually focal and are referred to under the heading of Focal Symptomatology Mental disturbances occur in brain tumors but it is surprising how indistinct a relationship there is between the location of the tumor and the type or degree of mental disturbance These symptoms occur more prominently in frontal and temporal lobe lesions, in tumors of the corpus callosum, and also in cerebellar tumors, in which they frequently do not appear until after the removal of the tumor or the release of the increased intracranial pressure The mental symptoms are usually those of intellectual deterioration There are some confusion impairment of memory inattentiveness loss of initiative and dullness and late cases may go on to stupor



Fig 419 —Bilateral abducens palsy due to increased intracranial pressure (From Grinker Neurology Courtesy of Charles C Thomas Publisher Springfield Ill)

In summary therefore any patient either a child or an adult, who shows progressive development of neurological symptoms, should be regarded as a tumor suspect and if in addition signs of increased intracranial pressure make their appearance the diagnosis is almost certain, and treatment should not be delayed

Types —Gliomas form the largest single group of primary brain tumors and total about 41 per cent of these They have been classified by Bailey according to their predominant cell type and their malignancy generally depends on the embryonic character of the cells which predominate in them Glioblastoma multiforme (Fig 420) forms 30 2 per cent of the gliomas and is a very malignant tumor which usually causes death within a period of twelve months The onset and course are rapid in this type of tumor It

the nervous system to another by way of the subarachnoid space Consequently, tumors involving the nervous system may be single or multiple Pathological studies of these tumors in a large series of cases have been of great value This is particularly important from the standpoint of prognosis because statistical studies have yielded information from which the life expectancy of patients with different types of tumors can be determined Pathological classification has also been of value in affording data by means of which the type of tumor can sometimes be determined because of its location, or of the age of the patient, or the signs manifested, or the duration of symptoms

Intracranial Tumors

General Symptomatology—Brain tumors, being space occupying masses which gradually increase in size, usually have a clinical history of slow, gradual progression of signs Not infrequently, however, the patient will first become aware of his illness because of the sudden development of symptoms This may be due to vascular lesions, occurring in connection with tumor, or to the location and nature of the tumor Consequently the history of a slow, progressive illness, manifested by the signs of a single lesion, renders the patient a tumor suspect It must be borne in mind that brain tumors occur frequently in children, in whom they are usually located in the posterior fossa and consequently increase intracranial pressure rapidly The increase in size of the tumor, growing within the rigid, bony skull, will increase intracranial pressure and cause characteristic symptoms This is particularly true of posterior fossa lesions because the posterior fossa is a small chamber bounded by bone and tentorium, and also because pressure within it is easily transmitted to the channel by which cerebrospinal fluid escapes from the ventricular system

The signs of increased intracranial pressure are headache, vomiting, and papilledema The headache is not usually of localizing value, although in tumors of the posterior fossa it is usually located in the occipital region and down the neck The headache at the onset is often intermittent and occurs most frequently in the morning It increases in severity and finally may become continuous It is usually made worse by activity which will increase intracranial pressure such as stooping over coughing, or straining at stool It is often described as a bursting sensation Vomiting often accompanies the headache It is usually stated that the vomiting associated with increased intracranial pressure is of a projectile type, and that it occurs suddenly and forcibly and without nausea While this type of vomiting may occur especially in children with cerebellar tumors, the vomiting is usually associated with some nausea Papilledema is due to interference with the venous return of blood from the eye because of the increase in intracranial pressure The optic discs become edematous their margins are blurred the veins become tortuous and dilated the optic cups are filled in and exudate obscures the vessels and elevates the surface of the discs Early in its course it may be associated with very little change in visual acuity Papilledema unless relieved goes on to secondary optic atrophy and when this is complete, blindness results It has already been stated that increased intracranial pressure fre

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of adults and the cerebellum of children *These tumors are often cystic, grow* slowly and are compatible with an average survival of over six years They are more circumscribed than other gliomas Tumor tissue itself may form but a small nodule in the wall of a cyst *Sometimes areas of calcification occur* and these can be seen on x ray examination Astroblastomas form 5 1 per cent of the group and occur in the cerebral hemispheres of adults They have an average life expectancy of thirty seven months from the onset of symptoms Cysts are not common in this tumor but do occur The cells in it have sucker feet attached to blood vessels and there is a marked proliferation in the adventitia of the blood vessels Oligodendrogliomas form 4 per cent of the group and are solid tumors which occur in the cerebral hemispheres of adults Usually there is some calcification in these tumors so that they also may be detected on x ray examination They are slow growing and compatible with many years of life Spongioblastomas form 4 7 per cent of the group and occur along the cerebral axis in young adults or adolescents They are frequent in the optic chiasm and brain stem Their location makes them difficult to approach Ependymomas (Fig 422) form 3 7 per cent of the group and occur chiefly in children and about the ventricles They are *slow growing, but owing to their location, they are not compatible with* long life Calcification frequently appears within the tumor Pineal tissue is derived from neuroepithelium and pinealomas form about 2 per cent of this *group of tumors* *They may occur at any age but are most common in young* males in whom they cause precocious puberty and paralysis of upward conjugate movements of the eyes in addition to signs of compression and of increased intracranial pressure Ganglioneuromas *form* only about 0 4 per cent of this group and are made up of glia cells in all stages of development, and neurocytes, many of which are adult types with Nissl bodies These ganglion cells may be multinucleated Neuroepitheliomas are rare tumors in the brain but occur in the retina and spinal cord

Meningiomas constitute about 13 per cent of intracranial tumors They are also called dural endotheliomas and meningeal fibroblastomas They are composed of specialized connective tissue cells resembling those which form the arachnoidal villi, and it is probable that they arise from these structures They grow slowly are encapsulated and excellent results follow their removal They arise most commonly along the anterior half of the superior *longitudinal sinus along the course of the middle meningeal vessels in the* olfactory grooves and in the regions of the lesser wing of the sphenoid and the tuberculum sellae They may be large and lobulated or flat The capsule usually is very vascular and this makes removal of the tumor difficult In addition the scalp and overlying bones are usually vascular as well The cells are often arranged in whorls which may become hyalinized and calcified and are then referred to as psammoma bodies They may cause erosion and proliferation of the skull The increased vascularity the calcification and the changes in the bones of the skull may all be apparent on x ray examination and thus indicate the type of tumor that exists This tumor, which is of mesodermal origin does not invade the brain tissue but compresses it

occurs almost always in the cerebral hemispheres of adults, and infiltrates widely Within it there may be areas of hemorrhage, degeneration and cyst formation It is made up of cells of many sizes and shapes and many mitotic figures and multinucleated cells can be seen There is no single predominating cell The blood vessels are abnormal, and hemorrhages and thromboses may occur This type of tumor may show few symptoms even though quite large and the onset of those symptoms may be sudden Medulloblastomas (Fig 421) form 12 6 per cent of the group and usually occur in the cerebellum of children

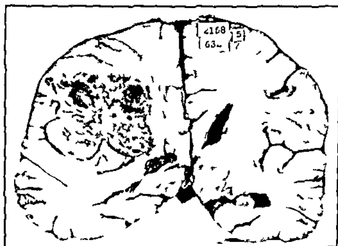


Fig 420 — Glioblastoma multiforme of the right parietal lobe

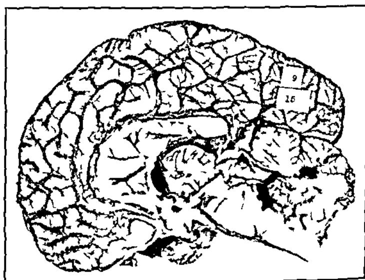


Fig 421 — A midline medulloblastoma of the cerebellum

This tumor metastasizes in the subarachnoid space Because of its location it bulges into the fourth ventricle and usually causes hydrocephalus Cerebellar symptoms may not be severe and may be limited to trunkal ataxia The early manifestations of the tumor may be regarded as due to a disturbance of the gastrointestinal tract and their true nature may not be appreciated for some time Astrocytomas form 37 per cent of the group and occur in the cerebrum

their dural envelope to extend into the intracranial cavity Hypophyseal duct tumors (Fig 424) are also called craniopharyngiomas adamantinomas and tumors of Rathke's pouch, and form 4 5 per cent of all intracranial tumors They occur particularly in children and arise from squamous epithelial rests within the hypophysis They are suprasellar, usually cystic and frequently become calcified, so that they can be seen on x ray examination in their typical location They may also be found in adults They are composed of epithelial cells of ectodermal origin



Fig 423 —Erosion and enlargement of the sella turcica caused by pituitary adenoma

Blood vessel tumors form about 2 0 per cent of all intracranial tumors They are composed of two types, the angiomas which are malformations and have been referred to on page 1111 and the hemangioblastomas which are true neoplasms Angiomas are frequently associated with vascular abnormalities elsewhere such as in the face or scalp They are made up of tangles of tortuous vessels the walls of which are pathological They occur most commonly in the cerebrum although the cerebellum and brain stem may be involved The vessel walls are sometimes calcified Sometimes a bruit can be heard by the patient and by the examiner on auscultation of the head Hemangioblastomas occur almost exclusively in the cerebellum and are usually cystic They are sometimes associated with angiomas of the retina and cysts of the pancreas and kidney and the condition is then known as Lindau's disease This disease is familial and on x ray examination calcified rings may be seen

Perineurial fibroblastomas, as the name indicates, arise from the sheaths of nerve roots or nerves They occur particularly on the auditory nerve, and in that location form about 9 0 per cent of intracranial tumors They produce the symptoms characteristic of involvement of the cerebellopontine angle They usually occur in middle aged adults and grow slowly They are usually unilateral and occasionally bilateral, but in the latter case they are more likely to be lesions of von Recklinghausen's disease which is a different entity

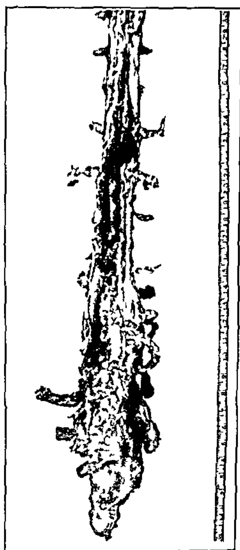


Fig 4 —An ependymoma of the cauda equina

They compress the structures in the angle in which they lie and produce characteristic symptoms (see page 1016) They are composed of elongated spindle shaped cells with ovoid nuclei

The common pituitary tumors are adenomas which form about 17 0 per cent of intracranial tumors They occur primarily in young adults and they produce characteristic endocrine disturbances which are described in Chapter XIV As they grow they erode the sella turcica (Fig 423) and break through

body The extent of this paralysis will depend upon the location and the size of the lesion It has been explained how the leg is represented uppermost in the motor cortex and the face lowermost In paralysis associated with a frontal lobe tumor the arm is frequently involved most The facial paralysis which may occur is of the central or supranuclear type with involvement of the corner of the mouth and not of the muscles of the forehead Mental symptoms may be present or may be absent and it is surprising what little mental disturbance may follow complete removal of the frontal lobe anterior to the motor cortex If there is no constant weakness or paralysis there may be a transitory impairment of function on the opposite side of the body fol lowing Jacksonian epileptic attacks In cases with hemiplegia the gait is that typical of the condition The knee is held more or less stiffly extended and the foot somewhat plantar flexed so that in walking the patient has to circum duct the entire leg to lift it from the ground even with this movement the toes usually scrape along the ground If the involvement is in the dominant hemisphere and near the Sylvian fissure aphasia usually of the motor type, will occur Tumors on the inferior surface of the frontal lobe in the olfactory groove cause anosmia

Temporal Lobe In temporal lobe lesions also Jacksonian convulsions may be present and these have been described Otherwise the tumor may cause but few focal symptoms Frequently mental disturbances and confusion occur The visual or optic radiations are usually involved and this leads to a hemianopic or quadrantic loss of vision in the opposite visual field When the tumor occurs in the dominant hemisphere there is usually aphasia involving all spheres of speech This is particularly true in left sided tumors in right handed individuals but not uncommonly right sided tumors in left handed in dividuals will not cause aphasia Visual hallucinations occur also in temporal lobe tumors whereas in occipital lobe tumors visual phenomena of a positive nature are usually limited to flashes of light Dreamy states and the typical uncinate fits described on page 1009 occur Extension of the tumor may cause contralateral paralysis

Parietal Lobe Tumors of the parietal lobe give rise to sensory disturb ances chiefly of the type of astereognosis and inability to discriminate between the texture size and shape of different objects The Jacksonian attacks aris ing from lesions in this lobe usually begin with sensory manifestations on the opposite side of the body Tumors of the parietal lobe may produce defects in the visual fields of the opposite side and also when located in the dominant hemisphere may lead to some aphasic disturbances

Occipital Lobe The most constant sign in occipital lobe tumors is a con tralateral homonymous hemianopia with sparing of macular vision (page 1000) In addition subjective visual phenomena may be present and may occur as part of a Jacksonian epileptic attack or not They consist of flashes of light or colors or stars in the opposite visual field Frequently also there is an aphasic disorder if the tumor extends far forward and this consists typically of a defect in reading and writing with minimal disturbances in other types of speech function

within the retina due to changes in the lesions there Papillomas of the choroid plexus form 0 5 per cent of intracranial tumors and arise from the choroid plexus in the fourth ventricle most frequently They have also been found in other parts of the ventricular system and they are most common in children They are formed of vascular cores covered by cuboidal epithelium The only manifestation may be that they periodically block the foramina in the ventricular cavities and cause headache which may be relieved by altera tion in the position of the head They respond well to x ray treatment

Metastatic tumors form about 5 0 per cent of intracranial neoplasms The order of frequency is carcinoma, sarcoma, hypernephroma The most common source of carcinoma is the lungs or bronchi and these give rise to about 30 per



Fig 4 4 —Calcification in the wall of a craniopharyngeal pouch cyst lying above the sella turcica.

cent of the intracranial metastases The primary source may also be in the breast, stomach, pancreas or prostate They are usually multiple and undergo degeneration and cyst formation They resemble the primary tumor and cause marked reaction in the brain Sometimes the carcinoma cells can be found in the spinal fluid Apart from the formation of metastases, carcinoma can involve the intracranial structures by direct extension from the naso pharynx

Focal Symptomatology—*Frontal Lobe* Lesions of the frontal lobe com monly cause Jacksonian epileptic attacks and the character of these has been described on page 1009 In addition because of impairment of motor path ways, there is usually a weakness or paralysis on the opposite side of the

body The extent of this paralysis will depend upon the location and the size of the lesion It has been explained how the leg is represented uppermost in the motor cortex and the face lowermost In paralysis associated with a frontal lobe tumor the arm is frequently involved most The facial paralysis which may occur is of the central or supranuclear type with involvement of the corner of the mouth and not of the muscles of the forehead Mental *symptoms may be present or may be absent and it is surprising what little* mental disturbance may follow complete removal of the frontal lobe anterior to the motor cortex If there is no constant weakness or paralysis, there may be a transitory impairment of function on the opposite side of the body following Jacksonian epileptic attacks In cases with hemiplegia the gait is that typical of the condition The knee is held more or less stiffly extended and the foot somewhat plantar flexed so that in walking the patient has to circumduct the entire leg to lift it from the ground even with this movement the toes usually scrape along the ground If the involvement is in the dominant hemisphere and near the Sylvian fissure aphasia usually of the motor type will occur Tumors on the inferior surface of the frontal lobe in the olfactory groove cause anosmia

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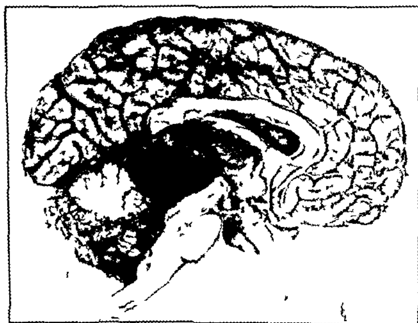
The Third Ventricle. Signs referable to the third ventricle may be caused by tumors within the ventricle, by invasion from tumors about the ventricle, or by compression, as in pineal tumors. Intermittent headache is frequently a common symptom and may sometimes be relieved by changing the position of the head, or by a sudden movement of it. This is explained on the basis that the tumor within the third ventricle intermittently blocks the escape of cerebrospinal fluid, and causes temporary increase of pressure within the proximal part of the ventricular system. Commonly also tumors in this location will produce somnolence of a characteristic type which resembles that of narcoleptic attacks. The patient may fall asleep while in the midst of any occupation or while at rest. The sleep is apparently a normal one and the patient can be aroused from it. Sometimes also there are disturbances in body temperature, and hyperthermia is frequently a serious complication of operations in this region. There is a close physiological relationship between the pituitary gland and the floor of the third ventricle, in the region of the tuber cinereum, so that endocrine and metabolic disturbances of a similar character are produced by lesions in these two regions. It has already been stated that in this part of the brain the head centers for the sympathetic and parasympathetic nervous systems are located, and Penfield has described disturbances of these functions occurring as epileptic phenomena in a case of tumor of the third ventricle. These so called diencephalic autonomic epileptic attacks were manifested by changes in peripheral circulation and in sweating.

Tumors in the region of the optic chiasm produce a bitemporal hemianopsia which was described on page 998. Gliomas directly involving the chiasm may produce irregular defects in the visual field and also primary optic atrophy. By extension forward, they may involve the nerves to the external ocular muscles and produce paralyses of these with diplopia and strabismus. Sometimes they produce dilatation of the optic foramina. Tumors of the pineal gland (Fig 425 and Figs 367 and 368) may show signs of involvement of the third ventricle, and are frequently associated with precocious puberty in young boys. They also cause increase in intracranial pressure and by involvement of the roof of the midbrain paralysis of upward conjugate deviation of the eyes and sometimes other ocular disturbances. Tumors of the thalamus may produce a typical syndrome consisting of a partial loss of sensibility on the opposite side of the body, pains and paraesthesiae on the opposite side of the body, and an exaggerated response to sensory stimulation in the involved area. Sometimes partial hemiplegia and abnormal movements on the opposite side of the body occur. The sensory disturbances are more typical than the motor ones and sensory stimulation of the skin causes disagreeable and painful sensation.

Tumors of the Pons and Medulla. The symptoms in tumors of these regions will depend upon the cranial nerve nuclei and the projection pathways that are involved. The fifth, sixth, seventh, eighth, ninth, tenth and twelfth cranial nerves may all be involved and usually the disability is bilateral. Various combinations may be picked out or the involvement may be entirely on one side. The pyramidal and sensory pathways in the brain stem may

also be affected If the tumor is unilateral the cranial nerve paralysis will be homolateral and involvement of the pyramidal tract will lead to a hemiplegia on the contralateral side Tumors arising in the brain stem show signs of increased intracranial pressure only late, but tumors within the fourth ventricle, on the other hand, produce increased intracranial pressure very early Cerebellar symptoms commonly occur from involvement of the cerebellar peduncles

Cerebellum Signs of a lesion in one cerebellar hemisphere have been described already on page 989 *When the lesion is in the midline in the vermis* the difficulties are mainly in gait and station and the patient tends to stagger and sway as he walks The head may be held stiffly and the neck may be rigid Other cerebellar signs may be present, such as those that occur in hemispheral lesions but they are frequently absent These tumors early produce an increase in intracranial pressure and signs of this are added to the focal symptomatology From compression various cranial nerves may be paralyzed but the tracts in the brain stem are not usually involved until very late in the course of the disease



F 4 —A l rg pin lon a

Occasionally homolateral hemiplegia rather than contralateral hemiplegia may occur in brain tumors because of compression of the opposite cerebral peduncle against the free edge of the tentorium

The pathological findings that may be present on x ray examination in cases of intracranial tumor have already been discussed (page 1028) Erosion calcification bony proliferation and increase in vascularity may all serve as localizing signs In addition the pineal sand (normal calcification in the pineal gland) may be displaced and convolutional markings in the skull may

be evidence of increased intracranial pressure The various distortions and displacements of the ventricles which may be found when they are filled with air and then x rayed have been referred to Information of extreme localizing value may be given by this means Other accessory examinations, such as the labyrinthine tests may also yield important information

Electroencephalography, and its value in the study and localization of brain tumors is described in the section dealing with epilepsy (page 1153)

Treatment—The treatment of brain tumors should be directed by a neurosurgeon Removal of the tumor is often possible and in some cases may be complete The prognosis, while always serious, is often compatible with many years of active life In some cases x ray treatment is a valuable adjuvant to surgical treatment

Intraspinal Tumors

Intraspinal tumors may be extramedullary or intramedullary The extramedullary tumors are by far the more common and can be further subdivided into intradural and extradural Tumors of the vertebral column, such as sarcoma chondroma and metastatic carcinoma, cause neurological manifestations through compression of the spinal cord The great majority of extramedullary tumors are meningeal fibroblastomas and perineurial fibroblastomas whereas the intramedullary tumors are chiefly gliomas

Symptoms—The onset of symptoms in extramedullary tumors is usually slow and may extend over several months or even a few years Usually the first manifestation is pain and this is due to irritation of the posterior nerve roots Consequently it is located in the distribution of the roots and it may be unilateral or bilateral It is commonly described as a feeling of constriction or of a girdle and it is made worse by coughing, or straining at stool, or other measures which tend to increase intraspinal pressure Local pain and tenderness over the vertebral column also occur and these are particularly evident in tumors of the vertebral column itself As the tumor compresses the spinal cord it causes symptoms referable to this The first manifestations are those of a slowly developing spastic paralysis and the spasticity is usually a prominent feature of this The paralysis is of the upper motor neurone type and its distribution will depend upon whether one or both sides of the cord are compressed and at what level it is compressed Sensory impairment also occurs and this likewise is a level loss Frequently the sphincters are involved so that retention or incontinence occurs Bed sores and bladder infections are frequent complications If the anterior roots are involved there will be atrophy at the level of the lesion in its segmental distribution Flexor spasms of the legs are sometimes very troublesome to the patient especially at night If the tumor is on the posterolateral surface of the cord a Brown Sequard type of paralysis (see page 1018) is most likely to occur If it is in the midline the pathological manifestations will be symmetrical from the start In cases of tumors on the anterior surface of the cord such as chondroma pain is not a prominent symptom and segmental atrophy and fibrillation are likely to occur

Intramedullary tumors are much less common than the extramedullary type but differentiation clinically is often impossible and always difficult In these cases perianal sensation often escapes involvement and sometimes at the level of the lesion there is a dissociation of sensation such as occurs in syringomyelia *Root pains are not common although stiffness and pain in* the back frequently occur In tumors of the cord the paraplegia may be in flexion or extension (see page 1018)

The diagnosis of the level of an intraspinal lesion may be difficult and may depend almost entirely on an accurate interpretation of the sensory loss Examination of sensation in such cases must be a painstaking operation which requires the fullest concentration on the part of both physician and patient Charts of the segmental distribution of the spinal cord are shown on page 987 and it is by means of evaluating the symptomatology in terms of the anatomical facts that accurate topographical diagnosis is made

The use of roentgenograms and examination of the cerebrospinal fluid are of great value in the diagnosis of cord lesions X ray examination will show *the presence of metastatic growths when they occur in the vertebral column* and sometimes in intraspinal lesions erosions of the bone and widening of the interpedicular spaces may be seen In addition when it is necessary lipiodol may be injected and in the presence of a block will outline the level of the lesion The principles of the Queckenstedt test have already been described *(page 1027) and by means of this block in the cerebrospinal fluid circulation* can be shown In cases of block the fluid distal to the block contains an increase of protein In long standing cases of complete block the fluid in addition is yellow or xanthochromic and will coagulate spontaneously on standing (Froin s syndrome)

In lesions of the cauda equina pain and paresthesia are common symptoms The pain will often be in the distribution of the sciatic nerve and may be regarded as sciatica for some time With such tumors weakness and paralysis are of the lower motor neurone type and sensory loss will conform to the segmental distribution of the nerve roots involved Bladder disturbances generally occur and may begin early in the course of the illness

Prognosis —The prognosis in extramedullary tumors arising from the dura is very good that in metastatic lesions of the vertebral column is of course bad Sometimes an intramedullary tumor may be partially removed

Treatment —The treatment of cord tumors should be under the direction of a neurosurgeon The results are so gratifying in many cases that treatment should be carried out early and before paralysis becomes complete This early treatment is essential in order to prevent irreparable damage to the spinal cord and cord tumor cases should be regarded as emergencies

Neurofibromatosis

Synonym —Von Recklinghausen s disease

Definition —This disease is often hereditary and sometimes occurs in families It is probably related to the familial type of hypertrophic interstitial neuritis It is characterized by areas of cutaneous pigmentation multiple sessile or pedunculated soft or firm masses in the skin subcutaneous

be evidence of increased intracranial pressure The *various distortions and* displacements of the ventricles, which may be found when they are filled with air and then x rayed, have been referred to Information of extreme localizing value may be given by this means Other accessory examinations such as the labyrinthine tests may also yield important information

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involves the fibers in the commissure In this disease it is sometimes found that there is a dissociation of these two types of sensibility and frequently temperature or pain sensibility will be lost separately at different levels Because of the impairment of thermal sensibility, the patients may accidentally burn their fingers without being aware of it Occasionally, spontaneous pain will be complained of in the segmental distribution of the lesion As the lesion extends up and down the cord the area of loss of pain and temperature sensibility becomes widened but rarely extends below the tenth dorsal segment Extension into the upper cervical cord will involve the fifth nerve and produce the same type of sensory loss in the face As the lesion extends transversely in the cord, it involves other structures Extension to *the anterior grey horn will produce weakness and wasting of the muscles in* the segmental distribution usually in the small muscles of the hand This may lead to a "clawhand" deformity such as occurs in ulnar nerve paralysis The symptoms may be bilateral from the beginning or one side may be affected before the other As the disease progresses there is sometimes degeneration of the pyramidal tracts with signs of an upper neurone type of paralysis below the lesion From extension to the medulla weakness of the soft palate, pharynx and vocal cords may result, and sometimes other cranial nerves will also be involved There are frequently fibrillary twitchings to be seen in the distribution of the peripheral motor cells that are involved From atrophy and weakness of the muscles of the back, scoliosis frequently occurs Involvement of the lateral horns of grey matter produces vasomotor disturbances which consist of edema of the hands excessive sweating and sometimes Horner's syndrome Trophic disturbances such as Charcot's joints, atrophy of bone ulcerations and whitlows occur Other congenital anomalies may be associated with this condition, such as cervical rib Occasionally the course may be sudden, but usually it is very slowly progressive and may come to a standstill for some years If the condition is posttraumatic and associated with adhesive arachnoiditis there may be signs of partial or complete block with the Queckenstedt test

Pathological Anatomy—The cord is enlarged and the arachnoid may be thickened Within the cord there are cavities which extend a variable distance both *longitudinally and transversely The process begins most frequently* at the base of one posterior horn or in the center of the cord near the central canal Surrounding the cavity there is an area of gliosis

Prognosis—The condition is chronic and progresses slowly Remissions may occur so that it is stationary for years but there may be at any time a sudden intensification

Treatment—X ray treatment over the affected region of the spinal cord may bring about considerable relief Occasionally surgical treatment by decompression and incision of the cyst is necessary

Alzheimer's Disease

Synonym—Presenile dementia

Definition—Alzheimer's disease is a slow progressive dementia with focal symptoms such as aphasia and apraxia which begins between the ages of forty and sixty years The dementia is progressive and leads to loss of

nodules and enlargements of the peripheral nerves Lesions may occur in the peripheral or central nervous system or in the meninges Penfield and Young* have described the essential pathological changes as hyperplastic re actions of cells peculiar to the tissues involved and superimposed on, or sub sequent to, this the appearance of neoplastic growth of these cells Changes may occur in the bones and also deformities like those of elephantiasis may occur in the legs The neurofibromatosis may involve the cranial nerves, or the peripheral nerve roots or peripheral nerves and the symptoms will depend on the size and location of the lesions Frequently multiple cranial or periph eral nerve palsies occur and in addition there may be signs of focal brain or cord lesions Biopsy of an accessible lesion will indicate the pathological nature of the disease

DEGENERATIVE DISEASES AND DISEASES OF UNKNOWN CAUSE

Syringomyelia and Syringobulbia

Definition —A chronic disease characterized by formation of cavities in the cord, and sometimes extending into the medulla, and manifested clinically by segmental signs usually of a sensory nature and frequently by involvement of tracts in the cord

Etiology —The exact etiology is unknown The condition is believed to be due to a proliferation of glia in the region of the central canal of the cord and the formation of cavities by degeneration of these proliferated areas The gliosis and cavity formation are usually in the region of the central canal, but may extend into the white matter also It extends up and down the cord for a variable distance Sometimes other members of the family may show evi dence of developmental abnormalities Cavities in the cord may also follow trauma when this is associated with adhesive arachnoiditis and interference with the vascular supply to the cord Degeneration and cyst formation fol low this vascular complication and are usually situated in the posterior horn of grey matter

Symptoms —The condition begins in the second or third decade of life and males are more often affected than females The usual location is in the lower cervical and upper thoracic cord The most characteristic clinical find ings are those relating to the central position of the lesion in the cord It has been described how sensory fibers carrying pain and temperature sensibility enter the cord through the posterior nerve roots They terminate in the pos terior grey horns, and new fibers convey the sensation to the opposite side of the cord, through the anterior commissure ventral to the central canal A lesion placed centrally in the cord in the region of the central canal will there fore first interfere with transmission of impulses along these crossing fibers and will produce impairment of sensibility in the segmental distribution from which the fibers have been derived Furthermore the types of sensibility im paired will be those of pain and temperature The common distribution of the impairment is over the ulnar border of the hand forearm and arm and across the upper part of the chest and back The sensory loss will be present on one side, if the lesion is in the posterior grey horn and on both sides if it

* Arch Neur and Psychiat 23 320 1930

present The characteristic sensory disturbance is a loss of muscle or position sensibility and vibration sensibility, and ataxia results from this The mechanism of the ataxia is similar to that described under the heading of Tabes Dorsalis, but in posterolateral sclerosis the ataxic manifestations are complicated by the signs of pyramidal tract involvement Sometimes also other forms of sensation are impaired and analgesia and hypesthesia may be present in a "glove" or "stocking" distribution Motor manifestations begin gradually with fatigue of the legs dragging of the feet and finally a weakness which is progressive The knee jerks and ankle jerks may be increased or absent depending upon the relative degree of motor or sensory involvement In the same way some cases manifest rigidity and some flaccidity The plantar responses are usually extensor The symptoms are always more prominent in the legs and the arms may manifest only paraesthesiae The sphincter control frequently becomes impaired and trophic changes sometimes occur In addition to the symptoms of subacute combined degeneration the symptoms of pernicious anemia are usually present in varying degrees Absence of free hydrochloric acid in the stomach is a constant finding in pernicious anemia and the same is true of subacute combined degeneration even when this latter disease is associated with a hypochromic rather than a pernicious anemia Not infrequently the involvement of the nervous system occurs before the signs of anemia are obvious and the diagnosis of pernicious anemia may be made first by the neurologist who sees the patient Mental changes may occur, and may be of a confusional or an affective type Not infrequently symptoms of neuritis are combined with those of posterolateral sclerosis or completely overshadow them

Pathological Anatomy—There is extensive softening in the cord with large and small foci of destruction The neuroglia are also affected in this destructive process Lipoid products of degeneration in the focus are removed by compound granular corpuscles There is a feeble connective tissue response and in the areas of healthy tissue there is some proliferation of neuroglia The blood vessels are thickened and there may be secondary inflammatory changes going on about them Areas of perivascular necrosis and of chromatolysis occur also in the brain

Prognosis—With intensive treatment of the pernicious anemia it is possible to bring about improvement and to prevent progression in early cases When objective manifestations are marked little improvement is to be expected

Treatment—The treatment is that of pernicious anemia Intensive treatment of the pernicious anemia must be carried out (see page 54?) with the administration of the equivalent of at least 200 grams of liver extract a week Bed rest is necessary for the first few months of treatment and physiotherapy may be of value

Lead Encephalopathy

Etiology—Lead can reach the body from many sources It usually gains access through the gastrointestinal tract and may be ingested in food or drinking water or inhaled from face powder or snuff In addition children frequently ingest it by chewing painted articles Lead may be stored in the bones and liver kidney and nervous tissue for many years without producing

memory, intellectual deterioration, and personality changes Tremors and convulsions may occur The speech becomes slowed, dysarthric, and unintelligible

Pathological Anatomy—There are degeneration of the cortical ganglion cells and the presence of senile plaques in the cortex The brain is shrunken and the pia arachnoid usually thickened There is degeneration of the neurofibrils some of which break up and others agglutinate to form distorted, tangled strands

Senile Dementia

This is one of the manifestations of old age There is a gradual intellectual deterioration with impairment of memory, inability to grasp new ideas slowness in thinking, inattentiveness, and sometimes personality changes, such as egotism, irritability, and suspiciousness The impairment of memory is usually for recent events, while the events of the distant past are vividly recalled and regaled Judgment and reasoning are impaired, and imagined slights are greatly resented Focal evidence of cerebral degeneration occurs Tremors are common and spasticity and pyramidal tract signs frequently occur Sometimes the symptoms of paralysis agitans or pseudobulbar paralysis make their appearance

Pathological Anatomy—The brain is small and diffusely atrophied The convolutions are thin and the sulci are widened especially in the frontal region The ventricles are large because of the atrophy of brain substance, and the ependyma becomes granular Nerve cells are shrunken and atrophied, and many have disappeared Neurofibrillar degeneration, such as that which occurs in Alzheimer's disease is also seen There is also increase in neuroglia cells and fibers

Pick s Disease

Synonym—Lobar sclerosis

Definition—Pathologically it is manifested by circumscribed atrophy of one lobe or one hemisphere and usually involves the frontal or temporal region In advanced cases the entire cortex may show evidence of atrophy It usually occurs in the later half of adult life and lasts for some years before terminating fatally There are progressive dementia an impairment of speech and focal manifestations such as hemiplegia

Subacute Combined Degeneration

Synonym—Subacute combined sclerosis posterolateral sclerosis

Definition—A progressive disease affecting chiefly the posterior columns and pyramidal tracts in the spinal cord and producing paraesthesia impairment of position sensibility ataxia and paraplegia

Etiology—This condition is almost always associated with pernicious anemia Occasionally it occurs also with hypochromic anemia and with certain toxic and cachectic states

Symptoms—The disease is one of middle age and usually of slow onset Sensory symptoms appear first and at the beginning are in the nature of paraesthesiae, usually of numbness and tingling in the fingers and toes Sometimes pains which simulate lightning pains and girdle sensations are also

cases The intention tremor is absent at rest but when the patient attempts to carry out a movement tremor occurs and becomes progressively more marked as the movement continues Signs of bilateral pyramidal tract involvement practically always occur in multiple sclerosis They may not be present in the early exacerbations but some time during the course of the disease they appear



Fig 4 6—Section of the spinal cord from a case of disseminated sclerosis Pal Weigert stain The preserved fiber tracts have stained black. The grey matter is unstained except for a few fibers running through it. Multiple patchy areas of degeneration are to be seen in the white matter and as the sheaths lose their myelin in the process of degeneration they also do not stain

symptoms. If acidosis occurs for any reason this lead will be liberated and then toxic manifestations may arise. The administration of calcium either in food or as a medicine will serve to bind the lead again within the structures noted.

Symptoms.—Lead neuritis has already been described on page 1094. Cerebral symptoms due to lead may be manifold and show evidence of diffuse involvement of the brain. Acute lead encephalopathy is characterized by convulsions, delirium and coma, and is often associated with signs of increased intracranial pressure and, sometimes, focal symptoms. The differentiation from brain tumor may be difficult. In its more chronic form, lead encephalopathy will manifest mental changes and general systemic symptoms. The general symptomatology of lead poisoning is described in Chapter XXIII. Sometimes lead may produce the symptomatology of localized progressive muscular atrophy involving the small muscles of the hand.

Pathological Anatomy.—Buzzard and Greenfield regard the symptoms of lead encephalopathy as due to spasms of the arteries in the brain but, in addition to that, ganglion cell changes occur and meningeal irritation may be present.

Prognosis.—The prognosis is always serious, but with proper treatment acute manifestations may improve and complete recovery occur. Chronic symptoms are difficult to improve.

Treatment.—The treatment of lead poisoning is described in Chapter XXIII.

Multiple Sclerosis

Synonyms.—Disseminated sclerosis, insular sclerosis.

Definition.—A chronic disease usually beginning in young people and frequently showing remissions. There are patchy areas of demyelinization and gliosis throughout the nervous system and, as a result, the symptomatology is one of disseminated lesions.

Etiology.—The etiology is unknown, but the condition is believed to be due to an infectious or toxic inflammatory process. The disease is less common in America than in the British Isles and Europe. The age of onset is usually between 20 and 40 years. Males seem to be more frequently affected than females.

Symptoms.—Since the disease causes an irregular distribution and number of lesions, the symptomatology varies considerably in different cases. Although this is so there are certain groups of symptoms which are rather typical of the disease. The mode of onset varies. Sometimes there is a slow, gradual progression of certain neurological signs but frequently the onset may be manifested by sudden temporary symptoms. It is characteristic that remissions occur. These remissions are usual during the first few years of the disease, but later than this the symptomatology is more likely to be chronic and progressive. On the other hand remissions may last for years. Charcot's triad of symptoms is typical of multiple sclerosis but by no means always occurs. It may become manifest early in the disease or may not appear until considerable progression has taken place. This triad of symptoms consists of nystagmus, a scanning staccato speech and intention tremor. The speech is slow and slurred and scanning and resembles that which occurs in cerebellar

Symptoms—The ocular or the myelitic signs may develop first Some days or weeks may intervene between the two sets of signs or both may occur simultaneously Usually one eye is affected first and then the disease involves the other eye There may be a true optic neuritis or a retrobulbar neuritis Bilateral central scotomata occur and in severe cases blindness may be almost complete The impairment of vision may be hemianopic in distribution There is often severe pain in the eyes The spinal cord lesion is that of a myelitis with level signs of motor and sensory involvement and with loss of sphincter control There may be an increase of protein and globulin in the spinal fluid and an excess of cells which are usually mononuclear

Pathological Anatomy—There is demyelinization of the optic nerves and the spinal cord The usual location is in the lower cervical and upper dorsal region but the disease may be more diffuse Perivascular infiltration is present in the demyelinated areas and frequently elsewhere as well

Prognosis—The mortality rate is about 50 per cent which results from respiratory paralysis or infection of the skin or urinary tract Recovery is often remarkably complete Relapses do not occur Treatment is symptomatic

Myasthenia Gravis

Definition—A chronic disease which is manifested by extreme fatigability of muscles

Symptoms—The diagnosis is not ordinarily difficult There is an extreme fatigability of muscles which on repeated use may become temporarily paralyzed The muscles supplied by the cranial nerves are most frequently and most severely affected and for a long time the disability may be confined to them In the morning after a night s rest there may be no signs of disability but as the day wears on progressive paresis occurs Ptosis of the eyelids is almost a constant symptom (Fig 427) Muscles concerned with extraocular movements may fatigue in the same way so that diplopia and strabismus occur after their use and disappear after rest The muscles of mastication are easily fatigued during the eating of food The muscles concerned in phonation and articulation tire quickly when the patient talks Movement of the muscles of the limbs will tire in the same way The fatigability may become progressively worse until gradually a virtual paralysis exists Just as voluntary movement tires so does reflex movement fatigue and on repeated tapping of the tendons the reflex responses gradually diminish and finally disappear The response to faradic stimulation of the muscles shows the same phenomenon and this is called the myasthenic reaction of Jolly Pritchard* has described another abnormality in electrical reaction which is an example of Wedensky inhibition In the phenomenon of Wedensky inhibition rapid shocks cause a change in nerve endings so that they soon cease to transmit nerve impulses Pritchard discharges through the patient at varying frequencies a condenser at a potential of 18 volts Whereas with repetitive stimulation in a normal person a tetanic contraction occurs with a horizontal plateau of maintained maximum tension in myasthenia gravis the maximum tension is not maintained but falls off to a plateau at

* Brain 1933 58 Proceedings p 3

Absence of the abdominal reflexes may precede other manifestations by a long period of time This is followed by the appearance of a plantar extensor reflex on the two sides and the gradual development of signs of a spastic paraplegia Bladder disturbances occur commonly and may be either retention or incontinence From involvement of the medulla various cranial nerve paralyses may ensue Retrobulbar neuritis is one of the most common manifestations of the disease and first shows itself by a pallor of the temporal halves of the optic discs With this there may be transitory periods of blurring of vision, but complete blindness rarely occurs Scotomata, enlargement of the blind spot and other visual field defects may be present Sensory symptoms are not prominent and it has been said that permanent sensory defects do not occur In most cases paraesthesiae are present at some time, most often in the form of numbness Objective sensory disturbances are usually of position and vibration sensibility and sometimes other forms are impaired as well Hemiplegia and localized areas of atrophy also occur occasionally The exacerbations early in the disease may consist of transitory symptoms of sudden onset or the subacute development of symptoms that persist for some time These may later disappear, during a remission, and when further exacerbations occur, the distribution and type of neurological symptoms may be different In long standing cases which have progressively become worse, all of the signs mentioned above are usually present The most characteristic change which occurs in the spinal fluid is the precipitation of colloidal gold in the paretic zone, and this happens in about one half of the cases The total protein is usually normal

Pathological Anatomy —Scattered throughout the nervous system there are greyish patches of demyelinization which are visible macroscopically (Fig 426) In the early stages there is no damage to the axone and this explains why few clinical findings may exist in the presence of many lesions The areas of degeneration affect principally the white matter, but may occur anywhere and in any size In older lesions the axones are fragmented and destroyed, and glial proliferation leads to scarring In some cases there is perivascular infiltration and because of this the condition is often regarded as an infection or inflammation of the central nervous system The prognosis varies not only may the disease run a long course but remissions may last a long time The usual course is one of gradual progression The average duration of life is about eight years

Treatment —There is no adequate nor specific treatment for the disease Various empirical measures have been used including silver salvarsan liquor arsenicalis vitamin B_1 potassium iodide and pyretic treatment but none of these seems to help

Neuromyelitis Optica

Synonyms —Diffuse myelitis with optic neuritis disseminated myelitis with optic neuritis

Definition —A form of subacute encephalomyelitis which runs a self limited course and is characterized by optic neuritis and myelitis

Etiology —The condition seems to be closely related to disseminated sclerosis except that it runs a limited course and has no remissions It is a rare disease

lower than maximum tension This falling off increases with increased frequency of repetition Remissions and fluctuations in the course of the disease occur and a remission may last for many years The disease ordinarily begins in the third decade and siblings may be affected Involvement of the respiratory muscles is very serious and may lead to sudden death

Pathological Anatomy—There is frequently a persistence or hyperplasia of the thymus In some cases a thymic tumor has been found There is an infiltration of the muscles and the thymus gland with collections of small cells resembling lymphocytes These are called lymphorrhages The glandular elements in the thymus may also proliferate Lymphorrhages have also been found in other organs

Prognosis—The prognosis is variable The onset is usually gradual and ocular manifestations such as ptosis and strabismus may be the only signs for years In some cases where more widespread involvement has existed a remission may occur and leave as residuals only the ocular symptoms

Treatment—The condition is most effectively treated by the use of prostigmine It is believed that myasthenia gravis is due to excessive action of choline esterase upon acetylcholine at the myoneural junction Choline esterase is an enzyme normally present in the body which destroys acetylcholine and prostigmine lowers the level of the former in the blood As a diagnostic test prostigmine solution (1 2000) may be given subcutaneously or intramuscularly in doses of 3 to 5 c c At the same time atropine sulfate in doses of 1/100 or 1/150 of a grain should be given to prevent the hyperperistalsis and abdominal discomfort produced by the prostigmine Within a short time of the injection a startling improvement will occur and this improvement will last for a few hours (Figs 427 and 428) In the treatment of the condition prostigmine is given by mouth in doses of 15 mg 6 to 9 times in 24 hours The doses can be spaced so that the greatest effect is produced when it is most needed When this is given by mouth it is usually not necessary to use atropine although if abdominal discomfort results it can be relieved by tincture of belladonna in small doses When the respiratory muscles become involved it may be necessary to place the patient in the Drinker respirator and at the same time to use prostigmine subcutaneously

In many ways myasthenia gravis and myotonia congenita (see page 1047) are physiological opposites In the former repeated use of the muscle results in rapid fatigue whereas in the latter there is difficulty in muscular relaxation preparatory to movement and repeated movement of the muscle quickly overcomes this difficulty Furthermore prostigmine which benefits myasthenia aggravates myotonia and quinine which benefits myotonia aggravates myasthenia

Progressive Muscular Atrophy and Amyotrophic Lateral Sclerosis

Definition—These terms are two of a triad which is used to describe the same disease but to emphasize the structures particularly involved Progressive muscular atrophy involves primarily the anterior horn cells of the spinal cord progressive bulbar paralysis involves primarily the motor nuclei in the medulla and amyotrophic lateral sclerosis signifies involvement both of the anterior horn cells and of the Betz cells in the pre Rolandic motor cortex



Fig 4 7—Typical facies of myasthenia gravis with bilateral ptosis and laxity of the muscles about the lip



Fig 4 8—The same patient as Fig 49 after administration of prostigmine

teriorized If, however, the flaccid atrophic paralysis in the arms is incomplete then the tendon reflexes may in some cases be increased The progress of amyotrophic lateral sclerosis is also slow

Pathological Anatomy—Various degrees of degeneration are found in the anterior horn cells many of which have disappeared Chromatolysis can be seen *in the swollen rounded out cells the nuclei of which are pushed to the periphery* and are degenerating Frequently excessive pigment is found in these cells The nerve fibers in the grey matter of the cord undergo degeneration and the fibers in the anterior roots also Astrocytic proliferation forms a diffuse scarring The involved muscles are also degenerated Similar changes occur in the motor nuclei in the medulla and in the Betz cells of the motor cortex and there is a secondary degeneration of the pyramidal tract fibers

Treatment—There is no specific treatment for the disease Rest nursing care and symptomatic treatment are indicated Recently promising results have been reported following the use of vitamin E (alpha tocopherol) in amounts of 300 mg or more per day It is the exceptional case however which has shown conspicuous improvement

Dystonia Musculorum Deformans

Synonym—Torsion spasm

Definition—A syndrome characterized by involuntary twisting movements which produce torsion of the limbs and trunk

Etiology—The etiology apparently may vary The disease is not common and has been reported following encephalitis lethargica other degenerative diseases of the basal ganglia and sometimes as a *familial disease*

Symptoms—In the familial cases the onset is usually early, occurring in childhood or adolescence The movements consist of rotation or torsion of segments of the body around their long axes *During the movements tonicity* is increased although it may be diminished at other times The movements resemble those of athetosis The postencephalitic variety of the disease may be associated also with signs of the Parkinsonian syndrome

Pathological Anatomy—Degeneration in the lenticular nucleus in the corpus Luysii and other locations has been described

Prognosis—The familial type is usually fatal within one to six years although cases of survival for as long as thirty years have been described

Treatment—Tincture of stramonium in 10 minim doses three times a day and gradually increasing to 40 or 60 minims three times a day may be of value in some cases Section of extrapyramidal pathways in the anterior white columns of the spinal cord is a new procedure the value of which has not yet been definitely established

Torticollis

Synonym—Wryneck

Definition—Spasmodic or continuous contraction of the cervical muscles producing a rotated attitude of the head It may occur in organic disease of the nervous system and also as an hysterical condition In organic disease it may be regarded as a limited form of torsion spasm It occurs as a symptom

These different types may occur separately, but usually one progresses into the other until all three exist Thus the disease may begin as progressive muscular atrophy, and in the course of its development show signs of amyotrophic lateral sclerosis and of bulbar paralysis The usual age of onset is between 30 and 45 years rarely it is familial Males are affected more often than females

Etiology —The cause is unknown

Symptoms —The disease develops very slowly with weakness and atrophy in the small muscles of the hands The process is usually symmetrical and the thenar eminences and interosseus muscles are most severely affected Deformities of the hand result from contractures of the unaffected muscles, and these vary in type The atrophy slowly spreads to involve the remainder of the muscles of the hands and gradually extends up the arms to the shoulder girdles The flexors of the forearm are usually involved before the extensors, and implication of the shoulder muscles causes difficulty in movement at this joint The deltoid is usually severely affected Movements of the head become weakened because of involvement of the muscles of the neck The atrophy may spread down the trunk and the disease tends to have a symmetrical segmental distribution Fibrillary twitchings occur in muscles which are not completely paralyzed These are due to irritation of the neurones during the slow process of degeneration and consist of fine, rapid, flickering movements in individual muscle fasciculi Voluntary movement or tapping the muscle may bring these out if they are not otherwise apparent Since this paralysis is due to a lower motor neurone lesion the reflexes are lost as the disease progresses Flaccidity is present and the faradic irritability is lost The disability advances very slowly over a period of years

When the process passes upward to involve the motor nuclei in the medulla the condition of bulbar paralysis is produced In this disease there is difficulty in articulation in swallowing and in phonation and these disturbances are known respectively as dysarthria dysphagia and dysphonia The tongue becomes atrophied and weak and fibrillary twitchings can be seen in it The vocal cords are paretic and the soft palate is atrophied and paralyzed Respiratory and cardiac symptoms may occur The masseter and facial muscles may also become involved With bulbar paralysis of this type the patient cannot properly chew or swallow food he cannot move the tongue about in the mouth to keep the latter clean he cannot clear his mouth of mucus and deposits of food and he cannot clear his throat by coughing and expectoration The result is that general nutrition is greatly disturbed and aspiration pneumonia commonly occurs

In the amyotrophic lateral sclerosis type of the disease the same segmental atrophy, weakness and fibrillations occur Symptoms previously described are present and in addition there is a spastic paralysis of the legs from involvement of the cells in the motor cortex and degeneration of the pyramidal tracts This has all the signs of an upper motor neurone lesion As far as the arms are concerned they have already been involved by a lower motor neurone lesion, which has affected the final common pathway and consequently the superadded symptomatology of amyotrophic lateral sclerosis cannot be ex

a posterior rhizotomy of the trigeminal nerve by which operation sensory fibers can be divided and motor fibers left intact

Sphenopalatine Neuralgia—This is characterized by pain in the eye across the face, behind the ear and radiating into the occiput and down the neck It is sometimes difficult to differentiate from trigeminal neuralgia and cocainization of the sphenopalatine ganglion may be necessary as a therapeutic test If this succeeds in abolishing the pain, alcohol injection into the ganglion can be carried out

Glossopharyngeal Neuralgia—The type of pain in this neuralgia is similar to that in trigeminal neuralgia It usually begins in the side of the throat and radiates down the neck and to the back of the lower jaw Sometimes it may begin deep in the ear Swallowing or protruding the tongue may induce an attack The treatment is surgical and consists of interrupting the afferent pathway of the painful sensation in the glossopharyngeal nerve

Sciatica—Sciatica is manifested by pain in the distribution of the sciatic nerve It may be due to neuritis or to neuralgia It is usually secondary to some other cause such as arthritis, anomalies of the lower lumbar vertebrae disease of the spine or pelvis back strain pelvic conditions and unknown causes The onset may be severe but is usually gradual For a time there is only slight pain in the back of the thigh particularly after exertion or if the leg is held in certain positions The severity of the pain increases and it radiates down the leg Pressure on the middle of the thigh, in the gluteal fold and at the sacrosciatic notch causes tenderness The leg is held flexed at the knee so as to ease the tension on the nerve The ankle jerk is sometimes diminished or lost The condition may be intractable and last for months Recurrences are common The treatment consists of rest strapping the back the use of heat and analgesics fixation of the legs and diathermy Any contributing causes should be removed if possible Injection of normal saline into the nerve sheath or into the epidural space through the sacrococcygeal canal may prove of benefit

In many cases chronic pain in the back and sciatic neuralgia follow rupture or dislocation of an intervertebral disc (herniation of the nucleus pulposus) *This usually occurs in the lumbar region and may be single or multiple* It sometimes follows injury to he back although in some cases such a history cannot be obtained On x ray examination in some cases the disc will be found to be narrower than normal and the adjacent vertebral bodies may have a scooped out appearance By means of the injection of air or lipiodol into the subarachnoid space and then by posturing the patient in a prone position it may be possible to show filling defects due to the protruding disc Sometimes weakness and atrophy of muscles in the segmental distribution corresponding to the level of dislocation may be found The treatment of this condition is surgical removal of the dislocated disc

In the treatment of sciatica the orthopedic surgeon may be called upon to play the chief role In addition to the eradication of the cause and bed rest, symptomatic treatment such as posturing warmth and the use of analgesics is of great value Epidural injection of normal saline and novocaine

in some extrapyramidal syndromes and is not infrequent as a sequela to encephalitis lethargica, in which case it is sometimes associated with the Parkinsonian syndrome

Symptoms—The rotation of the head is brought about by contraction of the muscles of the neck and the exact position which the head may assume varies in different cases The onset of the condition may be gradual or it may begin suddenly The rotation may occur as a spasmodic symptom or it may be continuous Frequently the patient will find that placing a finger on the jaw or in the mouth is sufficient to prevent torsion

Prognosis—If the condition is hysterical, proper psychotherapeutic measures should bring about relief If it is evidence of an organic disease the prognosis is bad In the organic cases, cutting the anterior and posterior nerve roots and the accessory nerves on the two sides may be carried out but the prognosis is still unfavorable

Neuralgia

Definition—Intermittent attacks of pain in the distribution of a nerve without evidence of organic disease of the nerve

Etiology—The cause of neuralgia is usually unknown, except in those cases where it is secondary to pressure or local inflammatory changes

Symptoms—The character of the pain varies The first attack is mild and subsequent attacks increase in intensity In the same way the attacks increase in duration Various agents may bring on individual attacks of pain such as local pressure or cold or movement Muscle spasms occur with the pain, but objective sensory changes are uncommon Reddening and sweating of the skin may accompany the attack

Trigeminal Neuralgia or Tic Douloureux—This type of neuralgia, which is one of the most common occurs in the face, in the distribution of the trigeminal nerve The branch most frequently involved is the second, but the disease may begin in, or spread to, the other branches The pain occurs in paroxysms and is usually described as stabbing or burning Usually trigger zones" occur in the face and touching these or exposing them to a draught will precipitate an attack of pain The pain is very severe and may be accompanied by a spasm of the face on the affected side and flushing of the skin, lacrimation and salivation The patient may go for long intervals of time without an attack The elimination of infections and the administration of bromides and analgesics may cause some improvement Usually, however, it becomes necessary to carry out some procedure which will interfere with the transmission of pain sensibility from the face to the brain The simplest procedure is the injection of alcohol into the peripheral branches of the nerve In the first division this is done in the supraorbital notch in the second division it is done in the infraorbital foramen and in the third division it is done in the mental foramen In some cases also avulsion of the terminal branches of the nerves in the same locations will bring about relief If these measures are not successful, the maxillary and mandibular nerves may be injected at the foramen rotundum and foramen ovale respectively Still other cases require

very frequently an increase in the number of attacks either before during or after menstruation Lennox and Cobb suggest the possibility of an explanation such as the following for the occurrence of convulsions We know that under sympathetic stimulation contraction of cerebral arteries occurs and we may assume that in epilepsy such contraction may occur Arterial spasms would lead to decreased blood flow in the capillaries This might lead to deficient oxygenation and consequently alkalosis of the brain tissue Under these conditions one might expect an increased passage of fluid outward through the capillary wall with resulting edema Some or all of these factors (oxygen lack alkalosis edema change in electrolyte equilibrium increased intracranial pressure) might stimulate nerve cells to the point of discharge with resulting muscular spasms Apnea and muscular contraction would result in a great accumulation of lactic acid and carbon dioxide in the tissues producing a condition of acidosis which would initiate a reversible reaction leading to a better utilization of oxygen a restoration of circulation and relief of muscle spasm

Symptoms—Epileptic attacks may be major or minor the so called "grand mal" and "petit mal" The difference in these two types of attacks is one of severity Major attacks are usually accompanied by loss of consciousness and by convulsive movements or other symptoms of a disabling type Minor attacks on the other hand may pass unnoticed and may consist of merely a momentary pause and clouding of consciousness There are sometimes prodromal manifestations of an approaching epileptic attack so that relatives of the patient may know of its imminence Such prodromal symptoms may consist of irritability seclusiveness nervousness excessive appetite or some other change the presence of which has become associated with the occurrence of an attack In addition to this there is usually a warning to the patient or an aura that an attack is about to occur This warning may last but a moment so little time in fact that the patient cannot prepare for the attack which is to follow Frequent types of aura are feelings of a rushing sensation a "gone" feeling or a tremulousness arising in the epigastrium and moving up the body to the head Sometimes the aura may be felt in the extremities and may be in the nature of paresthesia Occasionally abdominal pain serves as a warning In addition to these generalized types of aura there are certain focal aura which have been referred to on page 1009 Following the aura the attack occurs It is frequently ushered in with a cry and the patient becomes cyanosed or pale and falls unconscious The limbs stiffen out for a short time and then clonic movements usually begin in the extremities. These movements may be limited or generalized During the attack the patient frequently bites the tongue between his clenched teeth and incontinence of urine is a common feature Frothing at the mouth is usually described and this froth may be blood stained if the tongue has been bitten Following the attack certain sequelae may be present for a variable length of time Occasionally focal signs such as a Babinski reflex will be present and these are much more likely to follow focal than general attacks Almost always the patient is drowsy and somewhat confused and usually if it is possible he will sleep for a few hours afterward The patient himself has no actual knowledge

through the sacral hiatus is used but is usually disappointing Injection of saline into the sciatic nerve should be *done only by one familiar with the* procedure

Epilepsy

Definition.—Epilepsy and the convulsive states are symptoms of disease and not disease entities To define these phenomena is a difficult matter, and Grinker describes them as recurrent paroxysms of convulsive movements sensory or psychic dysfunction, with or without loss of consciousness

Etiology.—Since epileptic phenomena are symptoms, they may be due to many causes It is probable that there is an inherent convulsive capacity in the constitution of the individual which makes him more liable to manifest certain diseases by this symptom In the presence of this convulsive capacity the occurrence of other complementary factors may result in the production of epileptic seizures These additional factors may be many Gross and microscopic changes in the structure of the brain are often associated with epilepsy Thus the condition occurs in cases of brain tumor, cicatrices of the brain, general paresis and a multitude of other organic diseases of the nervous system Physical and chemical factors may also precipitate attacks and these include changes in oxygenation, in acid base equilibrium, in edema of tissues and in the permeability of cell membranes The circulation is intimately associated with the production of these changes In addition, disturbances and diseases in other systems of the body are frequently accompanied by epileptic attacks

Pathogenesis.—The mechanism of the production of convulsive symptoms is that of a neural discharge at some level of the central nervous system. These discharges need not necessarily arise in the cerebral cortex, as convulsions may occur due to discharges in the spinal cord, as in strychnine poisoning, or in the diencephalon as described by Penfield The exact physicochemical processes which induce this discharge are not known but there is evidence to indicate that it is concerned with vascular phenomena acid base equilibrium and the metabolism of water and of electrolytes That a change in circulation occurs is attested by the fact that vascular phenomena take place in the cortex of the brain coincident with attacks It has been observed frequently that blanching of the surface of the brain often in a small area occurs immediately before an attack and then as the convulsion begins the blood vessels become congested and suffused By alteration in acid base equilibrium attacks may be induced or inhibited Alkalosis is able to produce attacks and this result is hastened if it is combined with overventilation or hyperpnea Conversely starvation and the maintenance of a mild acidosis may inhibit or even prevent attacks especially in children Contraction of pial vessels has been seen to occur during overventilation and alkalosis On the other hand the rebreathing of air with a high carbon dioxide content is often sufficient to stop an epileptic attack The alteration of the metabolism of water and electrolytes by forced hydration is also able to produce attacks Individual attacks may be precipitated in epileptic patients by undue exertion, mental worry the use of alcohol constipation and sometimes by other factors In women, there is

by the fact that they persist even in curarized animals in which the actual convulsion is prevented In subclinical or larval grand mal there are random isolated spikes, sharp waves of longer duration and also slow waves If the attacks are non focal these abnormalities will arise from many points but are not synchronized If the attacks do arise from a single focus such as in the cases of the gross structural lesions which we have discussed, there will be a phase reversal at this point and therefore the location of the focus can be determined At the present time there is some dispute as to whether a typical pattern occurs for psychomotor epilepsy and psychic equivalents Because of these disturbances in cortical rhythm Lennox has proposed the term cerebral dysrhythmias as a substitute for the term epilepsy

Personality changes and psychiatric symptoms frequently occur in epileptics These do not always bear relation to the duration of the disease to its severity nor to the amount of cortical atrophy that exists Personality changes are sometimes obviously dependent upon the restricted life that is forced upon the patient and the worries which his illness entails Apart from this however irritability seclusiveness suspiciousness, etc, commonly occur and these in some cases, become so marked as to necessitate institutionalization Not infrequently, the mental changes may be more severe, and progressive intellectual deterioration will occur and lead to dementia Epileptic patients with psychoses should be committed to an institution as they are likely to be dangerous if free in the community

Treatment—In those cases of focal epilepsy in which demonstrable focal, structural lesions occur in the brain the treatment consists of surgical removal of these Such treatment has proved very successful in a large series of cases published by Penfield Sympathectomy has not proved of value in the treatment of this condition

The chief medical treatment of the epilepsies is the use of luminal, or phenobarbital This is given in doses varying from one half grain to 2 grains three times a day The dose may be modified and given at whatever time and in whatever amount best suits the individual patient It is sometimes possible by giving a single dose of 1½ grains at night to control the attacks Luminal is effective in reducing and sometimes in stopping major epileptic attacks but its efficacy is much less in regard to minor attacks The medicine should be taken regularly and no single dose should be missed as this may be followed by an aggravation of the condition and even by status epilepticus Bromides are sometimes useful adjuvants to luminal but have the disadvantage that when used over a long period of time they lead to a skin rash In certain cases the use of thyroid extract in addition to the phenobarbital, has produced greater improvement and the dosage and continued use of this should be regulated by frequent determinations of the basal metabolic rate

A rigidly controlled program of dehydration has been adopted and recommended in the treatment of chronic epilepsy by Fay He recommends a total fluid intake of from 300 to 500 c c per 24 hours depending upon the severity and number of attacks This fluid intake is given in small amounts equally divided during the day so as to minimize the severe thirst of which these patients complain No sodium chloride is added to the dry diet The dehydra

to 3,000 6,000 c c in 24 hours or until a satisfactory attack occurs (5) Diet to contain considerable amounts of carbohydrates such as vegetables ice cream, custard, fruits, potatoes rice, candy, cereals, etc This may be divided into three roughly equal meals (6) Fluid intake and output to be carefully measured for each six hour period and charted against weight (7) Nausea dizziness, vomiting, weakness, dropping blood pressure, fainting, syncope to be particularly noted If these occur, the procedure should be stopped

X ray examination of the skull after the injection of air into the lumbar subarachnoid space or directly into the ventricles has already been referred to on page 1031 By this means it is usually possible in focal structural lesions to determine the location of the lesion Such a result, in cases with attacks suggesting the same focus, is an indication for surgical intervention It is frequently found both in the presence and absence of focal structural changes that the ventricular system is enlarged and that the brain shows evidence of diffuse atrophy either on one side or throughout (Fig 429)

More recently electroencephalography has been added to our methods of examination This method of investigation consists in recording electrically the waves of action potentials from the cellular areas of the brain and especially from the cerebral cortex In 1924 Berger described the so called alpha rhythm from the occipital cortex These rhythmical discharges occurred from 8 to 12 times per second and they were present when the eyes were closed They varied in amplitude in different individuals but they were constant in each individual If the individual opened his eyes or engaged in some mental activity such as anxiety or a mental problem, the alpha rhythm was blocked out Since that time investigations have gone on, and it has been found that in addition to the normal alpha rhythm which occurs in the posterior parts of the hemispheres there is a different sort of rhythm called beta rhythm which can be recorded from the anterior half of the brain This latter is of lower amplitude than alpha rhythm and it occurs more rapidly—about 20 to 30 times per second It is not blocked out by mental activity as the alpha rhythm is Disease processes cause changes in the amplitude rate and shape of these waves In subdural effusion and meningeal tumors for example where the brain surface is pushed away from the skull there is a depression of activity On the other hand in traumatic or degenerative cerebral lesions so called delta waves appear which are of greater amplitude than the normal and which occur from one to seven times per second

There are several types of abnormal wave produced in the epileptic state In petit mal for example there is the appearance of a sharp spike wave and of the delta wave just described and these abnormalities occur in rhythmic pattern They can be recorded especially from a basal lead attached to the posterior wall of the nasopharynx and it is likely that they originate at the base of the brain or in the hypothalamic region These sequences of spikes and slow waves appear at the rate of 3 per second In grand mal attacks rapid sharp waves of high amplitude occur in rhythm and they vary in frequency They seem to consist of a hypersynchrony produced by an excessive number of cells acting together That the tracings are not due to the muscular movements nor to afferent impulses arising from them is shown

by the fact that they persist even in curarized animals in which the actual convulsion is prevented In subclinical or larval grand mal there are random isolated spikes sharp waves of longer duration and also slow waves If the attacks are non focal these abnormalities will arise from many points but are not synchronized If the attacks do arise from a single focus such as in the cases of the gross structural lesions which we have discussed there will be a phase reversal at this point and therefore the location of the focus can be determined At the present time there is some dispute as to whether a typical pattern occurs for psychomotor epilepsy and psychic equivalents Because of these disturbances in cortical rhythm Lennox has proposed the term cerebral dysrhythmias as a substitute for the term epilepsy

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tion method in practical use has given less favorable results in the experience of others than those reported by Fay

In 1937 Putnam and Merritt began a series of experiments to determine the anticonvulsant powers of a group of old and new drugs They carried out their experiments by determining the electrical threshold in the cat, and then studying changes which might be brought about in this threshold by the administration of various drugs The well known anticonvulsants of course raised the threshold, and these included the bromides and phenobarbital

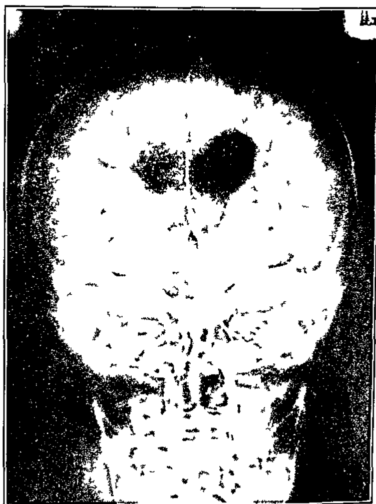


Fig 4 9 —Generalized cerebral atrophy in a case of epilepsy without a focal lesion obstructing the escape of cerebrospinal fluid from the ventricle The lateral ventricles and third ventricle are greatly enlarged symmetrical and in the midline

They found in addition however a small series of drugs which seemed to be of greater anticonvulsant effect than phenobarbital and which had relatively low toxic effect From this work the development of a new drug sodium diphenylhydantoinate (dilantin) arose and it has attained widespread use It is reasonably well tolerated by most patients who find it of considerable subjective as well as objective benefit It is a more effective anticonvulsant than phenobarbital and is accompanied by fewer depressing effects its toxic manifestations are relatively slight and many of them pass off spontaneously within a period of three or four weeks and it—like all other

anticonvulsants in common use—is much less effective in the treatment of petit mal than of grand mal It may be found that the effective dose closely approximates the toxic which is indicated by tremors nystagmus gastric discomfort and skin rashes A hyperplasia of the gums is apt to occur especially in children Other less common signs of toxicity are fatigue loss of weight emotional and physical excitability and hirsutism

Dilantin is usually given in doses of 1½ grains three to five times a day If given with meals its moderately unpleasant effects are diminished Usually a small dose of phenobarbital is continued Any changes in the medical treatment of epilepsy should be made slowly and gradually

In children the most efficacious treatment is by means of ketosis or acidosis, and this, in its own field, is probably the most satisfactory single means of treating epilepsy The diet is based upon the ketogenic antiketogenic ratio of the foods given The caloric requirements of the child are determined by the standard methods based upon body surface Sufficient protein is given to preserve nitrogen equilibrium and the balance of the caloric requirements is made up by the administration of carbohydrate and fat The ketogenic antiketogenic ratio should be three or more to one Carbohydrate is made up of 100 per cent antiketogenic element Fat consists of 90 per cent ketogenic and 10 per cent antiketogenic elements Protein consists of 58 per cent antiketogenic and 44 per cent ketogenic elements (according to Woodyatt s formula) At the beginning the ketogenic antiketogenic ratio may be gradually established Examination of the urine for ketone bodies, at regular intervals will indicate whether ketosis is being satisfactorily maintained

Migraine

Synonym.—Hemicrania

Definition—Paroxysmal attacks of headache which is usually situated in one side of the head and frequently associated with visual disturbances nausea and vomiting It may occur as an hereditary disorder

Etiology—The etiology of this condition is unknown It has been ascribed to arterial spasms and to localized cerebral edema Occasionally association of migraine and epilepsy has been described and these conditions are regarded as bearing some relationship to one another Women are more subject to the disease than men and it usually begins shortly after puberty

Symptoms—The attack may be preceded by prodromal symptoms Headache may be the only manifestation and usually involves the entire half of the head It is of a boring throbbing character Nausea is usually present and vomiting may occur In some cases the vomiting relieves the attack Visual phenomena frequently occur and are usually manifested in the opposite hemianopic field At the beginning they may consist of flashes of light or of an expanding bright spot and this is followed by blurring of vision or blindness in the involved field Paresthesia and weakness of the opposite side of the body may also occur The attacks are frequently associated with the menstrual period

Ophthalmoplegic migraine is a special form associated with ocular paralysis which may persist for days or weeks after the attack has subsided This occurs uncommonly and the diagnosis should be made with caution

Treatment —The subcutaneous injection of ergotamine tartrate 0 5 mg will often stop the attack Sometimes a second dose is necessary The drug is not as efficacious by mouth, but may be tried Emmenin, in doses of ½ to 1 drachm twice daily in the intermenstrual period, will also prevent attacks in some patients

Narcolepsy

Synonym —Gelineau's disease

Definition —A condition manifested by sudden irresistible attacks of sleep and sometimes by attacks of hypotonia associated with emotional outbursts and sufficient to make the patient fall to the ground (cataplexy)

Symptoms —Little can be added to the definition above The patient with this condition may manifest only narcoleptic attacks, or only cataplectic attacks, or a combination of both The last is the usual condition The narcoleptic attacks consist of an irresistible attack of somnolence The patient will go to sleep while in the midst of an occupation or conversation The cataplectic attack usually occurs when the patient's emotions are aroused and especially in the presence of pleasurable emotions Consequently, the phenomena often occur when the patient is induced to laughter The body musculature grows flaccid, the mouth droops open and the legs bend under the patient so that he slowly and limply sinks to the ground Consciousness is retained

Treatment —The best therapeutic results seem to follow the use of ephedrine The initial dose should be gr ¼ of ephedrine sulfate three times a day, and this may be increased if necessary Recently it has been found that benzedrene sulfate in doses of 10 mg, once twice or three times a day may also be of great value in the treatment of this condition If it is given late in the day this drug will produce insomnia It also tends to raise the blood pressure so that the condition of the cardiovascular system of the patient should be watched

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CHAPTER XVI

PSYCHOSOMATIC MEDICINE

FREDERICK R. HANSON, B.Sc., M.D.

INTRODUCTION

During recent years the term "psychosomatic" has appeared in medical literature with an increasing frequency and there is every reason to believe that the attention given to this phase of medical evolution will continue to increase. In spite of this increasing interest, or perhaps because of it, a considerable confusion has arisen not only about the meaning of the term "psychosomatic" but also about the basic changes in medical concepts involved in the acceptance of the role played by emotional stresses in the processes of disease. It is very difficult to give a clear comprehensive definition of the meaning of "psychosomatic" in a few words. For purpose of convenience in this book the term "psychosomatic medicine" will have the meaning of "An integrated approach to the study of disease which properly evaluates the psychological, somatic and environmental factors involved in the process of disease in the living person."

Although the term is relatively new, having been first brought into common usage by Draper as "psysomatic" in 1928, the necessity of studying and treating the person as well as the so-called disease has been recognized for over two thousand years. While the necessity of a holistic approach to the study of disease has been expressed frequently by many physicians during that time, such an approach has lain within the realm of the "Art of Medicine" until the beautiful studies of Cannon in 1908 first presented objectively the fact that there was a clear relationship between the emotional state of the animal and its physiological processes. Subsequent to Cannon's initial work an increasing number of animal and human experiments demonstrated clearly that emotional factors play a definite role not only in laboratory studies but in the disease process of the living human being as well. The scope of this book does not permit the detailing of these experimental and clinical studies, but they can be found in the standard texts and scientific periodicals on psychosomatic medicine.

During the latter part of the nineteenth century an equally important series of developments began to occur in the field of psychiatry. Prior to that time the studies of the human mind and emotions had been based upon concepts which were variously mystical, demonistic or religious in origin. Starting from his interests in the biological medicine of that time, Freud became increasingly aware of the fact that emotional factors played a powerful role in the life and well-being of the individual. It was forced upon him that these emotional disturbances were poorly understood but that, more importantly, it was possible to understand these disturbances in terms which were at once both logical and useful in therapy. The monumental investigations of Freud

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ways be considered normal for each individual or each environmental circum stance For example it may be entirely normal for a student to exhibit a mild diarrhea under the stress of an all important final examination whereas it would be entirely abnormal if he were to develop diarrhea each time he was subjected to the minor stress of being called upon to recite in the classroom, or if his diarrhea were to persist for months after the examination To state the matter another way if a small harmless snake were to crawl into a room one person might react with utter panic another with slightly fearful avoid ance and a third person walk over and pick up the snake It is obvious that this snake had an entirely different meaning for each of these individuals and that his reaction was based not just on the presence of a snake but much more importantly upon the psychological meaning of the snake to him By ex tending this concept it becomes apparent that the reaction of an individual to a given stimulus is dependent upon the psychological meaning of that stimu lus to the individual This concept is one of the utmost importance in the proper understanding of the psychological factors involved in psychosomatic medicine It immediately brings up the question "How then are these mean ings developed in the individual?"

To answer this question completely would take us deep into the fields of psychology and psychiatry and even now some of the factors involved are not fully understood It will be possible however to discuss some of the more salient features of this process particularly as they pertain to psychosomatic con siderations To begin with it must be recalled that when the infant is born into the world he is still entirely unequipped for independent existence He must depend upon others not only for food and protection and affection but even for life itself He is capable only of the most primitive metabolic and gross regulative processes of ingestion and excretion of food and fluids of incoordinate movement of primitive sensory discrimination and of crying His nervous system is only partially myelinated and he is incapable of co ordinated movement speech or verbal understanding He appears to be aware only of internal stimuli such as hunger and thirst and of external stimuli of a crude nature such as those productive of pain or gross discomfort Further more it is highly improbable that the infant in his early stages of existence can distinguish between what is external and what is internal in origin The only means of expression available to him are those of crying wriggling sleep ing and those are primarily of a reflex nature He must be cared for by a parent or some parent substitute if he is to survive

It must not be forgotten however that he brings with him certain biochem ical and structural mechanisms and propensities of an inherited and a con genital origin These mechanisms plus the unlearned reflexes constitute the basic reactive unit the infant Whether or not there are also present certain psychological propensities of a basic and individually unlearned nature is a matter of debate at the present time In any event more recent thinking has indicated that the biochemical psychological and reflex mechanisms present at birth and now considered instinctual may be subject to alteration by environmental influences both physical and psychological during the life of the individual

and his school, Janet, Bleuler, Jung, Meyer, and others made it clear that the human mind and emotions were provinces *open to the tools of scientific investigation*. It was this development in the knowledge of individual psychodynamics and the contemporary demonstration of the fact that the emotional *and physiological status of the individual were interdependent* which gave rise to the objective concepts of psychosomatic medicine.

Many misconceptions have arisen about psychosomatic medicine. To some it is a specialty; others believe that its concepts apply only to certain disorders and still others express the rather naive fear that its proponents believe that all disease is purely psychological in origin. None of these beliefs is correct. Psychosomatic medicine is, in simple terms, the correct practice of medicine, whether it be practiced by the general practitioner, the surgeon, the internist or the psychiatrist. It is essential in the correct practice of medicine that a proper evaluation be given to the role played by somatic, environmental, and psychological factors in every disorder and in every patient. No other approach can lead to clear understanding, accurate diagnosis, and successful therapy.

In order to exemplify this let us consider the disorder asthma. In most cases there is a *protein sensitivity*, *an abnormal biochemical mechanism* which is present in a variable intensity and which is often inherited. But this sensitivity is not in itself enough, for the individual must come into contact with *the antigen to which he is sensitive before an attack will occur*; thus we see environmental factors coming into consideration. Further, we find from observation that many of these individuals will have their attacks markedly *intensified or even precipitated by powerful emotional stress*. *The importance* of any one of these factors may vary considerably from individual to individual and may even vary markedly from time to time in the same individual. It is thus apparent that any clear understanding of the disease and proper diagnosis of the patient will involve consideration of the somatic (sensitivity), environmental (presence of exciting antigen), and psychological (intensifying or precipitating emotional conflicts) factors. Furthermore therapy *cannot* be effective without desensitization or removal of the antigen and alleviation of the related emotional stresses.

In consideration of the fact that the epidemiological and somatic factors of disease will be discussed in detail elsewhere in this textbook, the remainder of this section will be devoted primarily to the discussion of psychological considerations.

PSYCHOLOGICAL CONSIDERATIONS

It is implicitly recognized by most physicians that emotional disturbances may influence the many organ functions of the body. We are all familiar with *the blushing of the embarrassed young girl*, the pallor and cold sweat of fear, the urinary or bowel frequency of the student at examination time, the indigestion of disgust, and the apoplectic countenance of rage. These are all concomitants *of everyday living* and all may be perfectly normal phenomena. Although these psychophysiological phenomena are universally present in mankind in one form or another, it does not follow that their appearance must al

ways be considered normal for each individual or each environmental circumstance. For example, it may be entirely normal for a student to exhibit a mild diarrhea under the stress of an all important final examination, whereas it would be entirely abnormal if he were to develop diarrhea each time he was subjected to the minor stress of being called upon to recite in the classroom or if his diarrhea were to persist for months after the examination. To state the matter another way, if a small harmless snake were to crawl into a room one person might react with utter panic, another with slightly fearful avoidance, and a third person walk over and pick up the snake. It is obvious that this snake had an entirely different meaning for each of these individuals and that his reaction was based not just on the presence of a snake but much more importantly upon the psychological meaning of the snake to him. By extending this concept it becomes apparent that the reaction of an individual to a given stimulus is dependent upon the psychological meaning of that stimulus to the individual. This concept is one of the utmost importance in the proper understanding of the psychological factors involved in psychosomatic medicine. It immediately brings up the question: How then are these meanings developed in the individual?

To answer this question completely would take us deep into the fields of psychology and psychiatry, and even now some of the factors involved are not fully understood. It will be possible, however, to discuss some of the more salient features of this process particularly as they pertain to psychosomatic considerations. To begin with, it must be recalled that when the infant is born into the world he is still entirely unequipped for independent existence. He must depend upon others not only for food and protection and affection but even for life itself. He is capable only of the most primitive metabolic and gross regulative processes of ingestion and excretion of food and fluids, of incoordinate movement, of primitive sensory discrimination, and of crying. His nervous system is only partially myelinated and he is incapable of coordinated movement, speech, or verbal understanding. He appears to be aware only of internal stimuli such as hunger and thirst, and of external stimuli of a crude nature such as those productive of pain or gross discomfort. Furthermore, it is highly improbable that the infant in his early stages of existence can distinguish between what is external and what is internal in origin. The only means of expression available to him are those of crying, wriggling, sleeping, and those are primarily of a reflex nature. He must be cared for by a parent or some parent substitute if he is to survive.

It must not be forgotten, however, that he brings with him certain biochemical and structural mechanisms and propensities of an inherited and a congenital origin. These mechanisms plus the unlearned reflexes constitute the basic reactive unit, the infant. Whether or not there are also present certain psychological propensities of a basic and individually unlearned nature is a matter of debate at the present time. In any event, more recent thinking has indicated that the biochemical, psychological, and reflex mechanisms present at birth and now considered instinctual may be subject to alteration by environmental influences, both physical and psychological, during the life of the individual.

Whatever disagreements there may be over the hypothetical backgrounds of such complex matters as instincts and heredity, there is little disagreement about the observed activity and rapid progress of the infant, both physically and psychologically. In a short time he begins to respond selectively to move in a coordinated and purposeful fashion to be aware of his surroundings, and to identify individuals. Since he is fed, cared for and soothed by his mother or some mother figure, what is more natural than that his first awareness of a world outside himself and his first experiences of affection should be personified in his mother. Indeed there is strong evidence to indicate that the infant makes little differentiation in such apparently disparate manifestations as the satisfaction of being fed, warmth, affection, and mother. It must also be added that there is now evidence that the assuagement of hunger without the accompaniment of physical manifestations of affection can lead to serious psychological and physical disability for the infant. These points are of real importance in psychosomatic medicine and psychiatry because this equation of physical and psychological satisfactions contains not only the seeds of future emotional conflicts but also may be of considerable importance in establishing a permanent relationship between an emotional conflict and the physiological disturbance of a specific organ system, a point which will be discussed later in more detail.

In the earliest postpartum stage of the infant's development, a period of a year or more, the most important source of comfort and discomfort, satisfaction and dissatisfaction, is centered around the problem of feeding. Not only does his life and well being depend upon food, but when he is hungry he is uncomfortable and when he is fed he becomes comfortable and satisfied. In all probability the infant is aware of existence only in terms of his own feeling of comfort or discomfort at this stage of his development. As he develops he begins to equate being fed with the feeling of satisfaction and being hungry with dissatisfaction. With the increasing development of his perceptual senses and probably because there is some delay in the satisfaction of his hunger, he begins to become aware of the fact that being fed and being satisfied are dependent upon some agency outside of himself. This agency is the mother or some similar person. During this same early phase in development, observation of the infant indicates that he derives a considerable degree of satisfaction out of sucking and putting things in his mouth even when not hungry. Through the interaction of these various factors there gradually comes about a strong interrelation between oral activity, the satisfaction of hunger, the receiving of affection, and the dependence upon outside agencies personified by the mother. This earliest stage of psychological development is characterized by the term *Oral Phase*.

During this phase in the development of the infant there is reason to believe and evidence to support the theory that the infant looks upon himself as a sort of major god, the center of the universe, who has only to wish or need to have his wishes and needs granted. He is in his own eyes omnipotent. And why would he not be? When he is hungry he is fed, when he is wet he is changed, and when he is irritable he is petted and soothed; in short he is

presented with evidence many times daily that he has only to wish to have his desires granted. But beginning with minor delays in being fed and consequent need for the recognition of objects in the environment other than himself, his greater perceptive capabilities and more extensive range of activities tend to reinforce and develop the psychological differentiation between himself and the environment. With the increasing maturation of his central nervous system he begins to crawl and walk, to talk and to understand simple language, and with this increase in his abilities it becomes necessary for society to impose restrictions on his activities and conduct both for his own safety and for the peace of others. Society in this case is again usually personified by his mother and the most repetitive restriction placed upon him at this stage is usually that of bowel training. Not only must he learn to refrain from defecating whenever he so desires, but also he is required to defecate at specified times and places. He soon learns that compliance with these wishes of the parents leads to approval and affection, whereas failure leads to disapproval and the withholding of affection. Again he has begun to find and form an equation between his psychological needs and an organ function. It is common knowledge to all parents that bowel training seldom proceeds smoothly and that there is regression with physical stress such as illness, or psychological stresses such as jealousy or lack of attention. This phase of development is characterized by the psychoanalytic term *Anal Phase*. It must be added that the rich innervation of the rectum and anus tend to make the retention and expulsion of feces a pleasurable activity to the youngster, and he in turn unconsciously relates this pleasure to his bowel training and to the approval or disapproval of his parents. This discussion must not be construed as meaning that bowel training is the only psychological factor at work during this period of development; there are many others such as sibling rivalry, restriction of activities, testing of capabilities, jealousies and various other frustrations and demands. All of these factors obviously vary tremendously from individual to individual and the impact of them upon the child is equally varied both quantitatively and qualitatively. These variable factors are of importance in the development of the individual primarily because they constitute a threat to his goal, the undivided and exclusive possession of the attention and affection of his mother. Because of the close relationship usual within a family, the chief rivals for the affection of the mother are father and the siblings. This rivalry situation begins during the anal phase and continues during the succeeding phases.

As the child's control of his bowel activities increases, the importance of these activities as a mode of gaining attention and affection from the mother increases. It is usual for the child's urinary control to lag behind the control of the bowel; this and other factors tend to focus the interest of the child on the urinary processes and their demonstrable organ of function, the external genitalia. With this shift in interest to the external genitalia the pleasurable potentialities of these organs are usually discovered. This early genital activity is the forerunner of later sexual activity, but is still essentially autoerotic in nature. By autoerotic it is meant that the aim and object of this

pleasurable activity are contained in the child's own body. There is no external object for this primitive sexual activity. This phase of development is called the *Phallic Phase*.

Throughout the phallic phase there is an increase in awareness and exploration of its surroundings by the child. Rivalries become more intense and the demands for attention from the parent of the opposite sex become more compelling. The rivalries are directed towards sibling and towards the parent of the same sex, and they have as their goal the total possession of the attention and affection of first the mother and then the parent of the opposite sex. Since these demands are strong and since the rival parent is to the child a tremendously powerful figure, the psychological conflict engendered is one of considerable strength. In the average individual this conflict is usually resolved by means of an identification with the parent of the same sex. Thus the child gains its goal by proxy, as it were, and avoids the fantasied threat of punishment by becoming like its former parental rival. These complex situations are described in psychoanalytic terms as the Oedipus and Castration conflicts, and they are believed by many psychiatrists to be the major constellations in the unconscious forces later giving rise to the psychoneuroses. They may be of singular importance in some of the psychosomatic disorders which appear as the individual grows older. This, the *Genital Phase*, goes through a relatively long latent period during which sexual activity is at a minimum and continues until endocrinological functions produce the morphological changes of puberty, at which time the psychosexual activity once more increases.

As the child grows older, he becomes more and more active and the scope and number of his social contacts increase tremendously through the phallic and genital phases of his development. All through this period there is an ever increasing series of interests such as friends, school, sports, explorations of the manifold complexities of the world and people about him. Not only is there an acquisition of apparently new methods of reaction and new types of behavior, but also there is the resolution and repression of emotions, conflicts, and behavior patterns of earlier years. The successful resolution of these earlier conflicts and emotions is achieved primarily through the mechanism of *sublimation*, that is, the substitution of socially acceptable outlets for the more primitive and infantile drives which become socially unacceptable as the child grows older. However, it must be made entirely clear that this process of resolution is almost never complete in any individual, and the residual primitive and infantile drives and conflicts vary from person to person and range from a minor and relatively inconsequential proportion in some to the tremendously powerful and incapacitating conflicts in the psychotic. It is important to note that these infantile conflicts may never reach the level of conscious recognition by the individual, and if they do, they become repressed again into the unconscious. There they do not become inactive; instead they continue their disturbing and unacceptable activity, manifesting themselves in pathological psychological and physiological symptoms, recognizable anxiety, or character or behavior disorders or eccentricities.

Whenever the basic needs and drives of the individual are opposed by the dictates of reality and the individual is prevented from fulfilling these wishes in a manner satisfactory to himself a conflictual situation is established in psychological terms this situation is called a conflict The inevitable by product of a conflictual situation is anxiety Originally in the life of the child this reaction is one of fear that is the recollection of a past experience in which the attempt to gratify an impulse or wish has led to painful results to the child Primarily, the source of these painful experiences is external and frequently parental and we recognize the emotion of fear with its physiological concomitants as the resultant of a remembered or self evident external situation of a threatening nature Anxiety is internalized fear It is fear produced by inadequate or inappropriate stimuli it is usually proportionate to the stimulus both in intensity and duration and most importantly it does not lead to an appropriate adaptive solution In the process of the conversion of fear into anxiety the memory of painful consequences becomes detached from the external situation and becomes psychologically related to the drives or wishes which led initially to the painful experience Thus whenever that particular wish comes into play anxiety is activated With the passage of time and as the result of past experience, an attempt is made by the individual to inhibit the enactment of this wish which leads to pain This inhibiting process is given the psychological term repression As has been previously indicated this preventive mechanism is seldom successful and the forbidden drive must be discharged in a substitutive way such as through symptoms sublimation etc If it is not substitutively discharged with its physiological accompaniments the feeling of anxiety is experienced by the individual

It is probable that the concept of the unconscious is the most important single step in the understanding of the formation of the manifold and complex symptoms with which the individual may be beset In simple language the unconscious is that portion of the human mind which cannot be brought into direct awareness by ordinary means It must not be considered as a circumscribed portion of the brain or body it is rather a conglomerate mixture of forces repressed memories experiences and fantasies which maintain a constant although variable interplay with each other and with those elements which are not unconscious It is within the unconscious that much of the conflict between the basic drives of the individual the demands of reality and the dictates of society take place On most occasions the acting out of these basic drives is not allowed by society or reality and they are dammed back but the demands do not cease and as a consequence anxiety arises when they are in danger of becoming conscious In order to protect himself against this anxiety and frustration the individual keeps the conflict repressed in the unconscious For example when the young child wants a toy with which another youngster is playing he will demand it and if it is not immediately forthcoming will not hesitate to kick and bite to get the toy As he grows older he soon begins to learn that such actions not only produce retaliation from the other child but also and more importantly lead to anger punishment and loss of affection from the all important parents Therefore he

pleasurable activity are contained in the child's own body. There is no external object for this primitive sexual activity. This phase of development is called the *Phallic Phase*.

Throughout the phallic phase there is an increase in awareness and exploration of its surroundings by the child. Rivalries become more intense and the demands for attention from the parent of the opposite sex become more compelling. The rivalries are directed towards sibling and towards the parent of the same sex and they have as their goal the total possession of the attention and affection of first the mother and then the parent of the opposite sex. Since these demands are strong and since the rival parent is to the child a tremendously powerful figure, the psychological conflict engendered is one of considerable strength. In the average individual, this conflict is usually resolved by means of an identification with the parent of the same sex. Thus the child gains its goal by proxy, as it were, and avoids the fantasied threat of punishment by becoming like its former parental rival. These complex situations are described in psychoanalytic terms as the Oedipus and Castration conflicts, and they are believed by many psychiatrists to be the major constellations in the unconscious forces later giving rise to the psychoneuroses. They may be of singular importance in some of the psychosomatic disorders which appear as the individual grows older. Thus the *Genital Phase* goes through a relatively long latent period during which sexual activity is at a minimum and continues until endocrinological functions produce the morphological changes of puberty, at which time the psychosexual activity once more increases.

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lief that these activities are centered primarily in the frontal lobes. It is further probable that the central and controlling areas concerned with the peripheral physiological manifestations of the various emotions of a primitive variety are located in and near the hypothalamic area. Although accurate details are lacking, it is reasonable to assume that the cortex controls by inhibition or excitation the range and degree of activity of these hypothalamic centers. From the standpoint of the physiological responses to the various emotions it is evident from experiment and observation that the autonomic nervous system constitutes the major peripheral neuronal network in this chain. Through the autonomic system it is possible to affect all of the organ systems of the body. The chain of events is then that an emotion acting through the corticohypothalamic neuronal net and from thence through the autonomic system may influence any portion or organ system of the body. The body may be further influenced of course through voluntary and involuntary activity of the skeletal muscles under the control of the cerebral cortex.

Thus the mechanisms involved in psychosomatic disorders may be considered as divisible into three major spheres of activity: the corticohypothalamic or emotional sphere, the hypothalamic autonomic or neurohumoral mediating mechanism, and the local pathologic disturbance which consists of alteration in function or tissue or both. These considerations are important and also convenient diagnostically, therapeutically, and for the purpose of lucid description. It is not possible nor is it reasonable in discussion to separate the autonomic functions from the endocrinological and metabolic functions since they are so intimately and inextricably related; they are thus subsumed under the term neurohumoral.

There is much evidence of both clinical and experimental nature to establish the conditioned reflex as an important factor in the development and continuation of psychophysiological functions. One has only to think of the salivation and gastric hypermotility when the hungry man is presented with the sight, smell, or thought of food to exemplify this thesis. It is probable that this complex interrelation plays an important role not only in the establishment of the normal psychophysiological reactions but also in the pathological psychosomatic mechanisms as well. Moreover, it may be intimately involved in the problem of organ choice.

ORGAN CHOICE

Perhaps the most vexing question in the whole field of psychosomatic medicine at the present time is that of organ choice. Why does one individual who is attempting to rid himself of anxiety by means of symptom formation develop cardiac manifestations whereas another individual manifests gastric symptoms? This is indeed a difficult question and it must be plainly stated here that we lack the necessary knowledge to formulate definitive and comprehensive answers to this question at the present time. We can present reasonable approximations with some assurance and in this we are rather like the man who is staring through binoculars at distant hills on

must learn to suppress (i e conscious subjugation) these antisocial wishes and before long this constant suppression leads by complex unconscious mechanisms to the complete repression of such wishes and aggressive drives Because these basic drives are not inactivated by being made unconscious the child must find some compromise solution If he does not, intolerable anxiety develops This compromise may take the form of partially releasing this aggressive drive by means of sports or some similar substitutive activity, or he may express his anger by a regression to a more infantile form of behavior or he may develop symptoms of a predominantly psychological character (e g conversion phobias compulsions, etc), or physiological epiphenomena of psychogenic origin such as diarrhea, tachycardia, tremor, etc These physiological disturbances may or may not lead to tissue alteration It is one of the inexorable laws of human life that some outlet must be found for this dammed up anxiety

While most of the previous discussion has been devoted to the psychological development of the child and his conflicts it is not necessary to assume that these infantile conflicts are the sole and unsupported source of the symptoms and disturbances which appear later in life It is unquestionable that the process of living inevitably leads to conflicts disappointments fears, and frustrations These later conflicts may be entirely realistic and productive of anxiety such as the fear of death while in combat or they may gain power and become dangerous to the individual primarily by reinforcing or combining with the already existing conflicts of an infantile nature It must be added that this latter combination of conscious and unconscious conflicts is by far the most common in present day living although this opinion is debated by some schools of psychiatry Whatever the source or age of the conflict the same psychodynamic processes are believed to operate and be valid

In this greatly simplified discussion of psychological and psychiatric principles it becomes evident that each individual has his own characteristic set of reactions that the dictates of society and reality impose demands upon the individual which are often contrary to his basic wishes and drives and that these conflicting forces result in repression and the formation of unconscious conflicts which are laden with anxiety We have further seen that in an effort to evade or eliminate this anxiety the individual is forced to develop some compromise solution and that this leads either to some acceptable substitutive activity or to symptom formation Without going into detail it can be stated that this symptom formation is a neurotic solution and as such is never a satisfactory or entirely effective compromise it is thus self perpetuating although the manifest form of it (the symptom) may change with time The question now arises as to how and through what mechanisms can these emotions influence the physiological functions of the body?

PSYCHOPHYSIOLOGICAL MECHANISMS

It is entirely probable that the complex phenomena of thought and memory take place in the cerebral hemispheres mainly in the cortex and although such manifestations are probably diffuse there is evidence to support the be

lief that these activities are centered primarily in the frontal lobes. It is further probable that the central and controlling areas concerned with the peripheral physiological manifestations of the various emotions of a primitive variety are located in and near the hypothalamic area. Although accurate details are lacking, it is reasonable to assume that the cortex controls by inhibition or excitation the range and degree of activity of these hypothalamic centers. From the standpoint of the physiological responses to the various emotions it is evident from experiment and observation that the autonomic nervous system constitutes the major peripheral neuronal network in this chain. Through the autonomic system it is possible to affect all of the organ systems of the body. The chain of events is then that an emotion acting through the corticohypothalamic neuronal net and from thence through the autonomic system may influence any portion or organ system of the body. The body may be further influenced, of course, through voluntary and involuntary activity of the skeletal muscles under the control of the cerebral cortex.

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a foggy day. He can delineate the main hill masses with certainty, but because of the fog he catches only an occasional glimpse of the finer details. At present it is not possible to present any integrated and holistic formulation of the determinants of organ choice but some of the probable factors involved can be listed.

Hereditary and Congenital Factors.—It is evident that hereditary and congenital influences may encumber the individual with disabilities such as a malformed heart, an increased protein sensitivity, etc. These defective organs and functions will not only be predisposed to further trouble under the stresses of life but they may also become the target for physiological disturbances of psychogenic origin.

Accidental Factors.—The factor of chance may play a major role as a determinant. For example an accidental injury or infection during the course of an intense emotional disturbance may tend to become the focal point to which these pathogenic psychological forces become related. Thus these psychological factors may increase the severity of the symptoms, prolong their duration or cause a return of similar symptoms and disorders during a later period of anxiety.

Social Environment.—This rather inclusive phrase refers particularly to the family group and culture in which the individual lives. In many so called familial diseases there is a tendency for the physician to confuse hereditary transmission of the disorder and the emulation of some parental disorder by the child. There is an almost universal tendency on the part of the child to ape the mannerisms and characteristics of one of the parents, usually the parent of the same sex. This proclivity on the part of the child applies to the pathologic characteristics of the parent as well as to the desirable traits and patterns. The child wants to be like the parent in every respect. This attempt to be like the parent has its origins largely in the unconscious and its complex dynamics are described by the term identification. Examples of this process may often be seen in families which have a high incidence of some particular dysfunction such as headaches, ingestion, dysmenorrhea, etc. The process of identification may be of paramount importance in selecting the mode of discharge for anxiety and thus in time may lead to a constant pattern of psychosomatic dysfunction for a certain organ. "It runs in the family" does not necessarily mean that the disorder is hereditary. A similar mechanism may permit the individual to identify with a group with which he is closely associated and thus we may see an apparent epidemic of a specific psychosomatic disorder in a closely knit group such as a group of soldiers or in *racial and cultural groups not because of racial* determinants but because of the psychological resultants of social environmental stresses.

Iatrogenic Factors.—Some symptoms or disabilities may be initiated wholly or in part by the physician. For example an individual may seek consultation by reason of minor precordial discomfort and palpitation which are of psychogenic origin and he may be told by the uncertain or unskilled physician that "he may have heart trouble" or that "he has a weak heart." This unfortunate and authoritative confirmation of the patient's fears may

lead him to consider himself as a cardiac invalid and thus cause him to restrict his social and economic activities accordingly. In certain instances this may lead through various *complex psychophysiological mechanisms* to eventual tissue pathology and death.

Symbolic Equivalents.—Among psychoanalytic concepts that of "affect equivalent" or symbolic equivalent is the most important of the psychodynamic mechanisms which are directly related to psychosomatic medicine. In order to clarify this concept it is necessary to recall that *in infancy there is an almost complete equivalence between certain psychological and physiological reactions* accompanying hunger. The satisfaction of both of these depends upon the mother and they are so closely identified in the mind of the infant as to be almost indistinguishable. If conflicts which involve this relationship are established and repressed in infancy, then at a later date situations which threaten the security of the unconsciously overdependent person may be reacted to by means of gastric hypermotility, mucosal engorgement and hyperacidity. This almost literal "hunger" for affection and security when long continued may establish the gastric dysfunction which is the necessary precursor *to the development of peptic ulcer. Many other similar psychophysiological relationships exist and will be discussed later.*

Behavioral Factors.—It is common knowledge that neurotic conflicts may lead to minor or major deviations from the usually accepted norms of behavior. It is not common knowledge however that these neurotically *originated behavioral patterns may be the all-important factor in the repeated exposure to certain diseases and injuries.* For example an individual with powerful unconscious conflicts of a sexual nature may be driven to repeated and indiscriminate sexual relations, and he may thus contract a new *gonorrheal infection almost as soon as he has been cured of the previous attack.* In other individuals neurotic conflicts may lead them repeatedly into dangerous situations and thus predispose to a high degree of accident proneness. Variations of this dynamic mechanism could be multiplied almost *indefinitely and involve almost all bodily systems.*

We have seen that transient *emotional stimuli can produce important physiological changes of a temporary nature* and that the unconscious conflicts may act as persistent and insatiable stimuli. It is this quality of persistence and insatiability on the part of unconscious conflicts, even in the face of denial by reality, which leads to their importance *in the understanding of psychosomatic medicine,* for when they become related to physiological dysfunction, as they frequently do, their continuous although variable excitation of an *abnormal physiological function* may lead to permanent cellular and tissue alteration. This relationship may be schematically *illustrated as follows:*

Continuous unconscious conflict	Continuous physiologic dysfunction
Reversible cellular change	Irreversible cellular change

It must be noted further that any unconscious conflict may have its power as a stimulus strongly *reinforced both by* other unconscious conflicts and by current conscious conflicts and situations.

GENERAL CONSIDERATION OF THERAPY

It is desirable here to re-emphasize the general thesis implied and expressed above *that all disease has a psychosomatic component* It must be recognized that the role of the psychological factors with which we are concerned in this chapter and their relationship to the biologic and environmental factors involved in disease is not a simple one The psychological factors may be of primary importance in the etiology or they may exist as concomitants or they may appear as sequelae of any disease Not infrequently they must be given consideration in all three aspects *It is of the* utmost importance not only that the psychological factors be recognized but also that they be carefully evaluated in their relationship to the biologic and environmental forces active in each individual patient Not only must this evaluation be carried out during the initial survey of the patient but also it must be followed by careful and repeated re-evaluations during the stages of active therapy and convalescence It is an inherent property of the living animal that the dynamic balance of the biological psychological and environmental forces is constantly shifting, and particularly is this true throughout the full course of disease

In general the therapeutic aspects of psychosomatic medicine may be subsumed under three main headings

1 Biological Measures—e g, pharmacological, surgical and general supportive therapies
2 Environmental Measures—e g public health aspects
3 Psychological Measures—e g psychotherapy

All three of these therapies are interdependent to a certain degree but since the first two are discussed elsewhere in the book we shall concern ourselves primarily with the third category

It must be stated unequivocally that the first requisite of adequate psychological evaluation of the patient and subsequent effective therapy is a lucid understanding of the major principles of personality structure and basic psychodynamics Just as effective biological therapy must be based upon a sound knowledge of physiology and pathology so must appropriate psychotherapy be founded upon a clear conception of the basic principles of psychodynamics and personality structures It is unfortunately true that the knowledge of human psychology has not yet progressed to a point which permits a universal acceptance of a single schematization nevertheless there is a sufficient body of organized data to justify a wide acceptance of basic principles Psychiatry like all other branches of medicine is undergoing a constant growth and revision

In psychosomatic medicine as in all other branches of medicine where psychological factors are of concern the factors of primary psychotherapeutic concern are three the attitudes of the patient in relation to his disease the relationship of patient and physician and the attitudes of the physician An exhaustive discussion of these three considerations is far beyond the scope of this chapter and for detailed information about them the reader is referred to standard textbooks of psychiatry and psychotherapy some of which are listed in the bibliography In spite of this limitation it is of importance to indicate some of the more important features

Attitude of the Patient—In his approach to the physician the patient presents not only certain biological and symptomatological manifestations but also certain attitudes and feelings which may be of extreme importance in the proper evaluation and treatment of his disorder. These feelings and attitudes are for the most part not apparent to the patient himself, and where they are he considers them to be either unrelated to the disorder or at the most a direct result of it. Since these feelings are manifestations of his personality structure, which is in turn a product of memories and conflicts which are largely unconscious, this unawareness on the part of the patient should not be occasion for surprise. In general the patient is not aware of the existence of these painful repressed memories, and even when he is dimly aware of their existence he cannot comprehend the relationship of these conflicts to his *symptoms*. *As stated previously, these unconscious conflicts*, with or without reinforcement from reality situations, may be etiological in respect to his symptoms. In other instances these conflicts may produce concomitant psychological disorders which materially interfere with proper treatment. For example, the individual with a marked resentment of authority, arising out of strong unconscious hostility towards the father, may refuse to accept badly needed treatment because of the authoritarian role of the physician. Even where realistic fears arise in relation to a known disease, they may be powerfully intensified through becoming related to unconscious conflicts, and the same conflict may be at once etiological for the disorder and the source of the overcharging of the realistic fear.

Usually the patient looks upon his symptom or disease as a matter of chance misfortune or a visitation of Providence. He does not consider that *his psychological activities could have any real part in the process*, *and he may* actively resist or resent any implication that his symptoms are essentially psychogenic in origin. This is due in part to our present day social attitudes, in which neurotic disorders are mistakenly considered as being imaginary or somehow shameful. But more importantly the patient is psychologically incapable of accepting such an explanation directly because it disturbs his own defensive mechanisms. It must be remembered that these unconscious conflicts were originally repressed because they were painful to the individual and that any attempt to bring them into consciousness meets with immediate and powerful resistances. Furthermore, since the repression of the conflict did not remove the anxiety, it was necessary for the individual to find some outlet for the anxiety, and in the psychosomatic disorders the outlet chosen, even though relatively ineffectual and potentially dangerous, is a physiological disturbance or symptom. The resistances stirred up in the individual *can take the form* of evident anxiety, disbelief, anger, or an intensification of the symptom, to mention but a few.

To make more explicit one of the implications contained above, the patient is not only incapable of bringing unconscious material directly into consciousness, but also injudicious attempts on the part of the physician to make him do so, or to make him understand his unconscious conflicts by confronting him directly with them, may lead to serious psychological and physiological harm to the patient.

Relationship of Patient and Physician.—It is safe to state that no patient voluntarily consults a physician with a completely unbiased attitude. Even before he comes to the doctor he has formed certain concepts and feelings about this authoritarian figure he is about to consult. He believes consciously that he has chosen that particular therapist because of things he knows or has heard about him and his abilities. While these reality judgments exist as such, they are largely built upon the scaffold of the unconscious feelings and attitudes formed in childhood and augmented, decreased, or varied since their inception. These all-important unconscious attitudes of childhood are largely formulated upon his relationships and feelings towards his parents and he brings to and transfers upon the physician this complex mixture of dependence, love, hate, rivalry, or fear which characterized his earlier relationships with his family and particularly his parents. This means that the patient approaches the physician in the relation of child to parent and the wise physician unconsciously or consciously realizes this and makes use of it in his treatment of the patient. It must be emphasized that this relationship and transference of unconscious emotions of childhood origin onto the person of the doctor is an action of which the patient is entirely unaware and which, because of its unconscious character, he cannot possibly verbalize or express directly other than in terms of feeling and behavior. Every physician of experience has seen many examples of apparently unexplainable overdependence, sudden resistance, adoration, or strong hostility develop during his treatment of the patient. These apparently inexplicable attitudes are easily understood if the physician takes cognizance of the universal and powerful character of the transference relationship. In simple terms, *transference* means the unconscious investment of the physician with the emotions derived from the early familial relationship which persist in the unconscious of the patient. This transference relationship of patient and physician is not a static one; throughout the whole course of the treatment it is constantly changing with now one emotion dominant and then another. The skilled physician may intuitively sense these changes and alter his attitudes accordingly, but the sure handling of this very difficult problem must depend upon a clear understanding of psychodynamic mechanisms if it is to be uniformly effective. The correct interpretation of transference reactions and the proper utilization of this knowledge is by far the most difficult problem in the whole field of psychotherapy. It can be added that many of the temporary improvements in the condition of the patient and subsequent therapeutic failure of the same treatment are in reality merely manifestations of the psychological changes engendered by the transference relationship.

The relationship between the patient and physician is not a one-sided affair. It must be evident that since the patient invests the physician with the powerful unconscious feelings transferred from the parents, the role played by the physician in the feelings of the patient cannot be an emotionally neutral one.

Attitude of the Physician.—If the foregoing statements are correct, and there is excellent evidence that they are, it becomes axiomatic that the unconscious and conscious attitudes of the physician play an important role in

the patient physician relationship. Just as most of the patient's emotional responses to the doctor are based upon his unconscious experiences and conflicts, so are the physician's attitudes and reactions toward the patient derived from his own unconscious emotional constellations. Thus the needs and demands of the patient expressed in his attitude and behavior may produce powerful reactions in the therapist and materially alter his feelings and behavior towards the patient. Often this alteration in attitude and behavior towards the patient may go unrecognized by the physician because the changes are brought about by impact on conflicts which are entirely unconscious. Many errors in therapy are brought about by this mechanism, the *counter transference*. For example, the demands of the aggressive patient upon the therapist may lead the physician to hasten his examination in order to be rid of the annoying patient and thus cause him to overlook some rather obvious pathology which he would not have missed had he not hastened his examination. One of the commonest errors in medicine today is the repetitive search for organic causes of a symptom or disorder even though the physician is reasonably sure that the origin of the symptom is psychological. This procedure usually stems from the physician's own insecurity; he is fearful of the censure of his colleagues and patient if he should overlook some pathology and yet he will cheerfully pass by *ten times* as many neurotic disturbances whose consequences may be equally, if not more, serious to the patient. Or he may avoid an obvious diagnosis of a psychogenic disorder in order to avoid the loss of self esteem consequent upon the admission that he does not know how to treat it. Many other examples of the effect of the physician's unconscious and conscious attitudes upon the therapy of the patient could be given but these few should indicate the importance of the physician's attitude in the realm of therapeutics.

PSYCHOTHERAPY

A discussion of the actual technics of psychotherapy is beyond the province of this book; however, some of the more important features of such therapy may be considered under two descriptive headings which cover almost all of the field of psychotherapy, namely, expressive and suppressive therapy. It is implicit in any form of psychotherapy that the phenomena of transference and *countertransference* discussed above are an integral and important part of such treatment.

Expressive Psychotherapy.—The primary aim of this form of treatment is to relieve the patient's symptoms and anxiety by means of breaking through his defenses (resistances) and discharging the inappropriate and excessive emotions bound up in the unconscious pathogenic memories and drives. It is thus aimed at the relief of symptoms by the removal of their causes. Because of the fact that the underlying conflicts and resistances lie mainly in the realm of the unconscious and preconscious, and because of the patient's inability to tolerate anxiety in other than minimal amounts, and for other technical reasons, this process must be carried out in a carefully controlled step by step fashion. In general, expressive psychotherapy makes use of exploration, abreaction, interpretation, transference reactions, free association and related devices, but most subvarieties of this therapy do not exclude the con

temporary use of some supportive measures such as suggestion, re education, etc Expressive or deep psychotherapy is time consuming and technically complex and for this reason must remain largely a tool for the specialist in psychiatry

Suppressive Psychotherapy—Suppressive psychotherapy is often labeled supportive or superficial psychotherapy The latter term is misleading because the proper practice of such therapy not only must be based upon a thorough knowledge of psychodynamics but also may have profound effects upon the patient The results obtained through suppressive psychotherapy are frequently impressive and indeed it is not infrequently the method of choice in treatment when reality factors such as time, availability of therapy, psychological accessibility of the patient etc, govern the decision However the aims of suppressive psychotherapy are diametrically opposed to those of expressive therapy Whereas the latter tries to remove the underlying causes of the conflicts the former (suppressive) therapy aims at restoring the defenses and adaptive mechanisms of the patient so that he may suppress the causes of the symptom and regain his former controlled status In particular the therapist may attempt to aid the reintegration and strengthening of the patient's defenses by means of such methods as reassurance suggestion counseling re education inspiration alteration of noxious environmental factors increasing the number and type of substitutive outlets for anxiety, etc In his endeavors the physician may and should use the powerful forces of the transference situation to increase the efficiency of the measures chosen It is a melancholy fact however that these methods are used far too frequently without any clear concept of psychodynamics in general or knowledge of the patient's own background and dynamics in particular Such misguided use of psychological methods in treatment will be of no benefit to the patient at best and may lead to a serious intensification of the morbid psychological and physiological processes

Practical Aspects of Therapy—In psychosomatic medicine the general concepts of psychotherapy given in brief above have certain important practical applications Perhaps the foremost of these is that psychotherapy on a nonverbal level in the transference relationship begins with or before the initial intreview of the patient and continues throughout the entire therapeutic relationship Whenever possible it is highly desirable for the physician to begin his psychological assessment of the patient concurrently with the organic diagnostic procedure This can be done without great difficulty by giving careful attention to the degree and type of manifest anxiety behavior attitude of the patient towards his disorder and the physician the chain of verbal associations etc It may be and frequently is advisable to explore superficially the psychological background and the conscious fears and problems of the patient at the initial interview This must be done with some caution in order to avoid an undue mobilization of anxiety it is wise to avoid a too deep or persistent direct exploration of suspected areas of conflict even though they appear to be superficial The study of the patient's problems defenses, and reactions must proceed *pari passu* with the organic investiga

tion for the diagnosis of psychopathology is arrived at by positive measures and not by exclusion of organic disease

When there is a reasonable degree of certainty in the mind of the physician that the symptoms do not arise from organic pathology the patient must be immediately and authoritatively reassured about the absence of related organic pathology It must be made explicitly clear to the patient at the same time that emotional conflicts or nervous tension can produce such *symptoms as the patient complains of and that further exploration and treat*ment of a psychological nature will be necessary if the complaints are to be removed At the present time it is often wise for the therapist to assure the patient that disorders of psychogenic origin are not imaginary and the wise physician can profitably reinforce this view by illustrations from the patient s own experience e g blushing tachycardia from fear nausea and vomiting from disgust etc The physician must resist the temptation and the entreaties of the patient to prescribe something and above all he must resist the trap of prolonged and useless search for organic causation because of his own fears or insecurities Many patients have been done nearly irreparable harm through a psychological fixation on a given symptom or disorder by means of such unnecessary examination and re examination

When tissue pathology has been demonstrated and where psychological mechanisms are present in an etiological concomitant or secondary role psychotherapy may be not only advisable but even imperative if alleviation or cure of the condition is to be expected It is generally advisable that appropriate psychotherapy be implemented concurrently with such local or general biological measures as may be indicated With combined therapy of this type it is absolutely necessary that the patient have a clear appreciation of the role of each of these measures in his treatment The choice of methods of treatment both in biological and psychotherapy is a very difficult problem at times and the determination can never be made effectively except when based upon a secure knowledge of the biological psychological and environmental factors which constitute the frame of reference of that particular patient

SYSTEMIC CONSIDERATIONS

In the discussion of the psychological factors related to the diseases of specific organs symptoms and causes of a purely organic type will be omitted since they are considered elsewhere in the book Although psychological factors will be emphasized particularly in their etiological significance there is no intention to indicate that emotional factors are the sole agents of importance Even where there is some reason to believe that a disorder is of psychogenic origin organic mechanisms must furnish the intermediary channels of action and at times tissue alteration with resultant organic dysfunction may be the end result Moreover when dysfunction is of primary organic origin unrelated emotional conflicts may be intensified and become related to the disorder complicating the symptomatic reactions and increasing the degree of disability In no situation can we afford to neglect consideration of the disease from the combined viewpoint of organic psychological and environmental factors

RESPIRATORY SYSTEM

It is a matter of easy observation and common knowledge that the function of respiration is influenced not only by the normal physicochemical methods of control, but by emotional reactions as well. Each of us is familiar with the held breath of suspense, the rapid breathing of excitement and fear, the irregular sobbing of grief, and the deep sighing of perplexity and tension. All of these variations are normal phenomena when they do not exceed reasonable limits of intensity or duration. On the other hand, when the exciting stimuli, whether they be of an organic or emotional origin or a combination of both, are of an abnormal intensity or continue to act, striking symptoms and profound bodily changes may ensue. We are concerned here primarily with those of psychogenic origin, the organic pathophysiological phenomena are discussed elsewhere in the book. Although acute transient emotional disturbances may produce symptoms and disorders which bring the patient to the physician, it is far more common to find that the emotional conflicts which cause the symptoms are partially or deeply buried in the unconscious and are chronic in nature. The mechanisms involved in this process have been discussed in a general way in the preceding sections. Among the common symptoms which may be partially or entirely psychogenic in origin are the following.

Dysrhythmia.—Minor variations in the amplitude and frequency of respiration are normal and are the means by which an optimum gas tension is maintained in the blood. Emotional stimuli may provoke and continue marked alteration in the rate, rhythm or amplitude of respiration (see pages 330 to 333). Among the commonest forms of such respiratory disturbances are intermittent deep sighing, shallow hyperpnea, apparent dyspnea and mild stridor. Many types of psychogenically originated dysrhythmias have been demonstrated on respiratory tracings by Meakins, Christie, Alexander and Saul and others. Usually these alterations are the direct result of anxiety, however conversion, compulsion or tic-like mechanisms may produce similar symptomatic results. The underlying psychodynamic mechanism can be determined only by a study of the individual case. A psychogenically originated dysrhythmia may exist as such, or it may appear as a concomitant or sequela of an organic dysrhythmia.

Hyperventilation.—This symptom is a common one during periods of anxiety and is usually present in a minor form. However, it may progress to the point of producing tetany, syncope, or even convulsive manifestations in the susceptible individual.

Cough.—One of the commonest symptoms in the field of medicine is that of cough. While it is obvious that persistent cough must lead to a thorough search for underlying organic pathology, it is far too often forgotten by the physician that psychogenic factors may increase the severity of the cough, continue it long after the original organic source of the cough has disappeared, or even produce it without the existence of organic pathology. Some experimental evidence exists which seems to indicate that even in conditions where chronic cough is due to an initial organic pathology such as tuberculosis

psychotherapy may be of material benefit in lessening the severity of the cough. The persistence of a cough beyond a reasonable length of time after the disappearance of organic pathology always should lead to the suspicion that persistence of the cough is due to psychogenic rather than organic causes. This is particularly true when the cough is or becomes emetic in type. It is generally believed by most psychoanalysts that cough of psychogenic origin usually results from the individual's fantasy that he has introjected (ingested) some object which leads to a feeling of guilt and disgust. He is thus by means of the cough (or vomiting) trying to rid himself symbolically of this introjected object. There is much evidence in the literature to support these views.

Dysphonia.—The various forms of dysphonia such as aphonia, hoarseness, whispering, and undue vocal fatigue are not uncommon manifestations of conversion hysteria.

Asthma.—That the disease entity of bronchial asthma represents a clear-cut example of a psychosomatic disorder has already been discussed. Involved in the consideration of this disorder are the factors of sensitivity to allergens, the exposure to these allergens, and certain psychological considerations. The coexistence of a specific sensitivity and the exposure to that allergen are not enough in themselves to explain the occurrence of asthma, for it is well known that an individual sensitive to house dust, for example, may develop not asthma but urticaria, eczema, hay fever, or angioneurotic edema instead. Furthermore, there is definite clinical evidence that some individuals suffering from asthma and sensitive to a specific allergen may be completely freed of their asthma by means of psychotherapy and yet retain sensitivity, as measured by skin test, to the same allergen. There is further evidence to the effect that an individual sensitive to a certain allergen may have an attack of asthma precipitated by an appropriate emotional stress in the complete absence of the specific allergen. It is thus evident that psychogenic factors must play an essential role in the production of asthma in many if not all individuals.

1. The attacks occur as a reaction to the danger of separation, real or fantasied, from the mother. The place of the mother may be taken by some surrogate figure in the life situation of the individual. The therapist may come to represent such a figure to the patient during the course of treatment.

2. The attack is often a sort of equivalent of a repressed anxiety or rage. It is noteworthy that crying is rare in the asthmatic; the attacks tend to appear in its stead.

3. Situations which stimulate the fear of loss of the mother may be either a realistic threat or they may be a temptation, usually sexual or aggressive in nature and one which the mother would disapprove, that encourages the breakthrough of repressed impulses. Attacks were found to occur when the defenses against such impulses either broke down or were suddenly and severely threatened.

4. The task of mastering the fear of being left alone governs the patient's whole life.

5 There is a considerable variation in the character structure of the patients involved in these studies, but a lack of independence and a marked dependence upon the mother or some surrogate appeared to be common to all

6 In most instances it will be found that the mother tended to be pathologically overprotective often as a reaction to her unconscious wish to reject the child

Because of the multiple etiological factors involved in bronchial asthma it is evident that proper therapy will involve the determination of the implicated allergens, desensitization in many instances and adequate psychotherapy While deep psychotherapy would be desirable for many of these cases it is obvious that economic and time factors will prevent the universal application of such measures The so called "superficial" psychotherapy will be of material benefit to many of them and should be directed towards the establishment of a strong positive transference so that the patient can have the maximum dependence on the therapist Supportive measures may be of considerable use in attaining this end As the patient gains confidence in the physician it has often been noted that there is a tendency for him to "confess" partially repressed conflictual material and that following such confessions there is usually a marked amelioration of the disorder at least for a time

Pulmonary Tuberculosis—It must be stated at the outset that there is little reliable data on the psychosomatic aspects of pulmonary tuberculosis On hypothetical grounds it appears to be entirely probable that the psychological factors such as prolonged hospitalization separation from the family chronic invalidism etc may have profound effects upon the course of the disease and upon the subsequent life of the patient Whether or not psychogenic factors may be concerned in the etiology of this disorder remains to be determined

Tuberculophobia is by no means rare and the failure to recognize this fear in a patient may lead to an almost irretrievable fixation of this belief On the other hand prompt diagnosis and powerful reassurance may dissipate the belief in its early stages and thus avoid years of semi invalidism

Recurrent Upper Respiratory Infections—There are many well documented instances of the cure of the tendency towards frequently recurring colds and similar infections Such cases have usually been reported as occurring during or after psychotherapy for other conditions Little is known of the mechanisms involved but it is now beyond the realm of speculation that psychosomatic processes may be profoundly involved in at least some cases of recurrent respiratory infection

CARDIOVASCULAR SYSTEM

During the last few decades the development of an increasing accuracy of diagnostic procedures has made it apparent that at least 50 per cent of the patients who consult physicians because of complaints which they believe to be due to the heart are found to have no demonstrable organic pathology of the cardiovascular system Even when organic lesions can be proved approximately 30 per cent of the symptoms cannot be attributed to the organic pathology The studies of Dunbar indicate that from 60 to 98 per cent of pa

tients with various cardiac complaints or disorders have been exposed to cardiovascular disease or sudden death among friends or relatives, whereas in control studies the incidence is less than 40 per cent. It is thus not surprising that any symptom which the patient believes to be due to the heart should be equated in his mind with visions of pain, invalidism or sudden death. These fears are reinforced daily by tales of friends and stories in the newspaper. Not only do these experiences increase the fear and anxiety of the individual with cardiac complaints, but also they prepare a fertile field for the growth of symptoms of psychogenic origin.

As W. C. Menninger points out, no other organ is so intimately associated with the feelings of love and hate in our language as is the heart. While it is true that this "body language" is derived in part from primitive physiological misconceptions, it is equally true that everyday experience demonstrates the alterations of rate, rhythm, and force of the heartbeats which accompany strong emotions. In addition, we see visible evidence of neurovascular changes and observe clinically the changes in blood pressure which accompany the *emotions of fear, hate and love*. It should not be surprising then that when such emotions are frequently experienced or become chronic through neurotic dynamisms, there may result in certain individuals symptomatic manifestations or pathophysiologic phenomena which may lead eventually to tissue and structural alterations in the cardiovascular system. As in most psychosomatic disorders, these psychophysiological reactions are mediated through neurohumoral mechanisms, primarily the autonomic nervous system.

Numerous clinical psychiatric and psychoanalytic studies have indicated that the central psychological motif commonly associated with cardiovascular disorders is that of hostility and aggression. Usually these impulses are closely integrated with unconscious sexual conflicts of a primitive nature. *Not infrequently these unconscious sexual impulses directed towards one* or the other parent lead to partially or totally repressed hostile wishes towards the opposite parent. In the unconscious these hostile wishes tend to be envisioned in terms of total destruction of the opponent, and because of guilt reactions and the fear of retaliation, such wishes tend to produce profound fears of death in certain individuals. Through psychodynamic processes such as identification, the reactive mechanisms of the cardiovascular system become responsive to the stimulation of these emotional constellations of hostility.

Symptoms related to disorders of the heart due to organic lesions or due to psychophysiological manifestations may be considered under several main categories: (a) pain or discomfort in the precordial area, (b) dyspnea, (c) disorders of rhythm and tachycardia, (d) *murmurs, and (e) others such as* fatigue, giddiness, insomnia, etc. The pathophysiological manifestations of organic origin are discussed elsewhere in the book, but almost all of the above-mentioned symptoms either may be of psychogenic origin or may appear as psychological concomitants or sequelae of cardiac dysfunction.

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Pain or discomfort in the precordial area is a common presenting complaint exhibited by the patient with a heart disorder of an organic or psycho

genic origin. The differential diagnosis usually does not present great difficulty when a careful history is taken. Pain of an organic origin is usually directly related to exertion, whereas pain of psychogenic origin is in most instances found to be either partially or totally unrelated to physical exertion and is in fact often found to occur only when the individual is at rest. Moreover, the character and distribution of the pain described by the patient with a psychogenic disorder are most often atypical. He tends to locate the pain in the region where he believes that his heart lies, and there is seldom any radiation of the pain. Close questioning frequently reveals that the "pain" is in reality a sense of oppression or superficial hyperesthesia rather than of the type typical of angina pectoris, coronary occlusion, aneurysm, etc. Of the utmost importance is the fact that proper investigation will disclose the neurotic background and experiences from which the symptoms have developed. In many individuals the strong reassurance as to the absence of organic disease will lead to the disappearance of the pain. When true anginal pain occurs it may become much more difficult to assess the part played by psychological factors, for clinical and experimental evidence has demonstrated that alterations in the function of the coronary arteries may be produced by emotional stresses of a conscious or unconscious nature. Only careful psychiatric investigation can elicit these factors in the majority of such cases.

Dyspnea is an equally common complaint in cardiovascular disorders, and, as a symptom, the assessment of its origin rests primarily upon its relation to exertion. In the absence of cardiac asthma, when dyspnea is unrelated to physical effort it is highly probable that it springs from stimuli of a psychological nature rather than from organic cardiac pathology. Characteristically the disturbance of respiration will be found to consist of intermittent deep sighing breathing with complaints by the patient of an inability to get a full breath or of a feeling of pressure in the chest (see Fig. 333). Tachypnea and hyperventilation are seen at times as a neurotic cardiac complaint. In almost all cases the differential diagnosis between psychogenic and organic dyspnea can be made easily upon the basis of a careful history; respiratory tracings may furnish excellent corroborative evidence in doubtful cases.

Disorders of rhythm and tachycardia are often the basis of complaints referred to the heart by patients with cardiac disorders of psychogenic origin. Whereas a transient tachycardia is the normal accompaniment of passing emotional stimulation such as fear, anger, and excitement, the persistence of these emotions may lead to a chronic although variable state of tachycardia. It is usual to find such a condition in anxiety neurosis and neurocirculatory asthenia, and it is probable that the underlying emotional conflicts acting through the autonomic system and sinoauricular node produce this tachycardia (see page 373). A more common source of subjective complaint is that of premature beat or extrasystole. This is usually experienced by the patient as a sense of skipped beat or palpitation, and the sense of discomfort frequently reinforces the individual's belief that he is suffering from heart disease. In the absence of an organic lesion there is clinical and experimental evidence to indicate that emotional stimuli acting through the autonomic system may produce extrasystoles. Failure on the part of the physician to reassure the

patient as to the absence of organic heart disease or the injudicious use of medication "to decrease the irregularity" may serve to confirm the patient's fears of heart disease and thus increase the underlying anxiety and lead to an increased neurosis and invalidism. Bradycardia as a result of emotional stimulation occurring during dreams has been recorded. Although psychological factors may be related to some cases of paroxysmal auricular fibrillation and flutter, existing data do not warrant conclusions on this point at the present time.

Murmurs.—There is no evidence to suggest that psychological factors are of any etiological significance in the development of cardiac murmurs of either the organic or functional type. However, they may be of profound importance in the establishment or increase of disability by neurotic mechanisms. It is an unfortunate fact that in the mind of the laity a diagnosis of murmur has become nearly synonymous with cardiac invalidism; because of this it has become doubly important for the physician to assess and treat each case in terms of isolated phenomenology such as the presence of a murmur. *Insistence of full activity within the limits of the patient's capabilities and* strong reassurance will do much to counteract the tendency of the patient to drift into a state of invalidism.

Other symptoms such as giddiness, headaches, syncope, fatigue, weakness and insomnia may accompany organic disorders of the cardiovascular system. When present, they may be the result of morbid physiology arising from the organic lesion or they may be psychogenic in origin, or they may be the manifestations of a combination of the two causes. The role played by each factor usually may be determined by a careful history, but at times intensive in*vestigation is necessary to establish the source.*

While a thorough discussion of the psychodynamic constellations and psychophysiological factors involved in diseases of the cardiovascular system is beyond the scope of this book, some of the salient features may be mentioned.

Emotional Effects on the Normal Heart

Cardiac Neurosis.—Aside from the transient effects of normal emotions upon the normal heart, there is a large group of people who have a number of symptoms related to the heart which cannot be attributed to organic lesions. This symptom complex is generally referred to in the current literature as "cardiac neurosis." Although this condition would be described more accurately as neurosis with cardiac manifestations, the current nomenclature has become so firmly entrenched as to make a change improbable.

In this group of patients the symptoms complained of are most commonly pain, dyspnea, palpitation, precordial discomfort, fatigue, or some of the other manifestations discussed above. Often there are frankly expressed fears of heart disease, sudden death, invalidism *or work incapacity*, and usually the patient evidences manifest anxiety, although at times the anxiety is completely *masked*. *Characteristically the complaints are out of proportion* to the objectively observed disability, whereas the patient with an organic *heart disorder tends to minimize the degree of disability* which he experiences. In neurotic disorders it is unusual to find any objective evidence of a dis

ordered function of the heart other than a minor degree of tachycardia of a variable character, occasionally extrasystoles at times subjective complaints of precordial tenderness, or pulse lability with emotion Proper differential diagnosis must rest upon the history of a neurotic background, the relationship of neurotic cardiac manifestations to this background and to the current stresses and the absence of objective findings of an organic nature The diagnosis of cardiac neurosis must not be made solely on the basis of exclusion of organic disease

In general, psychogenic cardiac manifestations are found in conjunction with anxiety or with an anxiety neurosis and the major psychological conflicts involved in this process have been discussed above However in some individuals the only manifest evidence of anxiety will be that of the cardiac symptoms it is in such cases that one finds that the conflicts are of a totally unconscious nature and that the individual has successfully repressed every evidence of the conflict other than psychosomatic phenomena In this latter and numerically less frequent group, intensive psychiatric investigation may be necessary before the psychogenic origin of the symptoms can be made evident Whereas the majority of the cardiac neuroses are related to anxiety neurosis it is not uncommon to find phobic and, less commonly hypochondriacal obsessional or delusional processes at the root of the cardiac complaints The discussion of these psychodynamic mechanisms belongs more appropriately in the realm of psychiatry and psychoanalysis

Neurocirculatory Asthenia —This disorder which has been variously called neurocirculatory asthenia (see page 373) soldier s heart disordered action of the heart (DAH) nervous heart etc was described by Da Costa during the Civil War and is largely a disease of military life although it is believed to occur in civil life as well Although this condition is usually described as an individual entity most of the present day evidence points to the fact that it is in reality a form of the cardiac neuroses described above Neurocirculatory asthenia (NCA) is usually depicted as occurring in a thin, inadequately muscled asthenic individual who has a lifelong history of avoidance of strenuous and competitive exercise and who is often labeled as 'constitutionally inferior It must be kept in mind that the reason for avoidance of strenuous exercise and competitive activity and thus an inadequate development of somatic and cardiac musculature may be entirely neurotic in origin rather than constitutional in many of these individuals It is not uncommon to find a history of neurotic dietary limitations in these patients and this would of course tend to limit further their physical development and reserves

On a situational basis NCA patients may be divided into two major groups (a) those who develop symptoms under a minimal physical and emotional stress and (b) those who develop symptoms only under severe emotional and/or physical stresses The former tend to recover from their symptoms less rapidly when they are removed from the stressful environment and given adequate psychotherapy because as one might expect their more limited tolerance of stress is usually found to be accompanied by a more profoundly neurotic background In the second group recovery usually occurs

rapidly upon removal from the exhausting environment and with the institution of adequate food, rest and psychotherapy.

The main symptomatic characteristic of this group of patients which appears to differentiate them from the cardiac neurosis group is the response to exercise. Details of this abnormal response to exertion will be found elsewhere in this textbook. In general the differences between the exercise responses of the N.C.A. group and the cardiac neuroses group are quantitative but not qualitative. Varying degrees of exercise intolerance are frequently noted in patients proved to have a cardiac neurosis. Adequate explanation of the mechanisms involved in the abnormal exercise tolerance does not exist at the present time, but it appears probable that endocrinal and autonomic dysfunction may play an important role, and it is well established that emotional conflicts may profoundly influence both of these systems.

In a study of Wittkower's, it was demonstrated that none of the N.C.A. patients examined could be considered to be well adjusted emotionally. A major portion of those patients who exhibited gross neurotic manifestations prior to the onset of the effort syndrome indicated that phobic mechanisms were of prime importance in their disorder. In many instances this appeared to be related to claustrophobic reactions and this in turn with the feelings of suffocation complained of by the patient. Whereas the peptic ulcer patient is often concerned with problems of economic security and the colitis patient with matters of cleanliness and overtidiness, these individuals must deal with conflicts which revolve around aggression and the need to maintain rigid standards of ethics, morality and performance. More specific details about this heterogeneous disorder will be found in the references given.

Psychotherapy is the most important single consideration in the treatment of the cardiac neuroses and neurocirculatory asthenia. In many instances excellent results can be obtained without the use of formal verbal psychotherapeutic technics; in other cases orthodox verbal psychiatric methods will be required. Decision on this point can be made only after careful assessment of the depth and severity of the neurotic factors in each case. In all patients it is absolutely essential to assure the individual about the absence of an organic heart disorder as soon as reasonable examination has indicated this. In general the cardiac neurotic tends to overprotect himself and to restrict his activities unduly because of his fears about his heart. It is usually necessary for the physician to insist upon a reasonable amount of exercise and activity for such patients in order to limit the tendency toward invalidism. Reassurance as to the lack of danger in connection with symptoms experienced during activity will do much to assist in keeping the individual active. Unusual amounts of rest are warned against in these neurotic patients. Supportive measures of a general nature are discussed elsewhere in the book. Mild sedation may be useful when anxiety is prominent, but the tendency to use it routinely must be deprecated.

Emotional Conflicts and the Diseased Heart

Angina Pectoris.—It is generally conceded that the symptoms of angina pectoris are due to an insufficient oxygen supply to the heart muscle and that this insufficiency is due to a narrowing of the coronary arteries. This

narrowing may be of a transient nature and be the result of muscular contraction under the influence of the autonomic nervous system, or it may be the result of tissue pathology in the walls of the coronary arteries and thus be of a permanent character. There is clinical and experimental evidence which indicates that emotional stimuli acting through the autonomic nervous system may markedly alter the rate and volume of blood flow through the coronaries and produce anginal symptoms. The hypothesis of those who consider that emotional conflicts may play an important etiological role in the development of angina pectoris is as follows. Unconscious conflicts acting through the vegetative nervous system may produce coronary spasm and the disastrous symptoms and effects of angina pectoris in some individuals. Recurrent spasm may lead to petechial hemorrhages in the wall of the coronaries and thus eventually to permanent tissue pathology and death in others. While there is evidence of a subsidiary nature to support this thesis, the evidence is by no means complete, nor does it indicate that this is the sole method concerned in the development of angina pectoris.

Aside from the possible etiological significance of psychogenic factors, there is much evidence to indicate that when anginal symptoms have made their appearance from any source, marked degrees of anxiety usually appear. The anxiety may be a simple result of the very real fears of pain and death, but it may also be reinforced by the unconscious emotional conflicts of the individual. Whatever the source of the anxiety, it tends to increase the frequency and severity of the attacks and undoubtedly contributes to the progression of the disease by means of the psychophysiological coronary reflexes indicated above.

Psychiatric surveys of patients with anginal symptoms have indicated that the personality structure of these individuals is similar in many respects to that of those persons who suffer from coronary thrombosis. The average patient with either condition tends to have powerful conflicts over authority, but whereas the anginal patients tends to try to be as good as his superior and to imitate the father rather than trying to outdo him, the coronary patient tries to subdue and to be the boss of others. In the pursuance of authority both of these patients are driven to work almost compulsively and have little time for other activities. Their intense need to dominate and to control completely their own activities often leads them to disregard the advice of the physician and they usually attempt to disguise or reject any disabilities because it tends to interfere with their drive for dominance. In both disorders it is common to find a history of emotional shock preceding the onset of the disease; this shock often takes the form of cardiac death in a near friend or relative or it may result from reverses in the striving for authority. The picture presented above is a composite one and individual cases may show marked divergence from the pattern.

While psychotherapy is highly desirable, it must be undertaken with the utmost of caution, for overenthusiastic investigation may intensify underlying conflicts and lead to an increase in symptoms or even death. In more advanced cases it is often wise to depend on superficial supportive psychiatric measures, such as reassurance and advice about current problems, rather than

to attempt formal verbal psychiatric investigation and therapy. When formal psychotherapy is deemed advisable, it should be undertaken by a skilled psychotherapist working in conjunction with an experienced internist. One of the major therapeutic goals in these patients is the diminution of unreasonable fears and the re-establishment of hope.

Coronary Thrombosis.—The frequency with which traumatic emotional stress precedes the onset of coronary thrombosis by a short time and the high degree of similarity in the character traits of these patients strongly suggests that emotional factors may play an important role in the etiology of coronary thrombosis, at least in some cases. When emotional conflicts are active in this process, it is probable that they act through the autonomic nervous system to alter the coronary blood flow, the blood pressure, and perhaps the rhythm and rate of the heartbeat. Although these psychophysiological reactions have been directly observed in a few cases, adequate psychodynamic and psychophysiological formulations are only in a hypothetical phase of development at the present time. Further studies will undoubtedly clarify this problem in the future.

As indicated in the discussion of angina pectoris, there is a strong similarity of personality structure in the patients of these two groups. The major difference between the two appears to be mainly a quantitative variation in the realm of hostility; whereas the anginal patient tended to equal his rivals, *the coronary patient seemed to be more strongly driven to subdue and surpass.* In her study of coronary patients Dunbar reports that no patient was found to have a good relationship with the father, and it is probable that this rivalry represents the prototype of the continuing struggle to equal or surpass any authoritarian figure, particularly in the field of business. In the group of coronary cases there was a more than chance exposure to sudden death due to cardiovascular and other accidents in the males of the family, and we know that such an occurrence in conjunction with powerful unconscious hostile wishes towards that person usually leads to profoundly disturbing emotional conflicts. These problems of hostility are usually found to be much more completely repressed in the anginal and coronary patient than is the counterpart which occurs in the *patient with hypertension.* While these statistical findings are useful for theoretical purposes, *their application to the individual patient is limited because of the wide psychodynamic variation among individuals.*

The psychological sequelae and psychotherapeutic considerations involved in coronary thrombosis are the same as those discussed under angina pectoris.

Emotional Factors in Hypertension

In the following discussion we shall be concerned with emotional factors *involved in essential hypertension;* consideration of hypertension due to known organic factors, such as anatomical defects, primary renal disease, tumors, endocrine dysfunction, intoxications, etc., *will be omitted. It is conceded* by most observers that the chronic elevation of blood pressure in essential hypertension is the result of an increase in tonus of the *arterioles* of the body, particularly in the splanchnic area. Further, it seems probable that the later anatomical findings, such as the thickening of the arteriolar

walls increased heart size and others are a result rather than a cause of hypertension There are two major hypotheses as to the origin of this increase in arteriolar tonus The neurogenic theory holds that it is a result of an increased or disordered activity of the vasomotor centers while the humoral theory considers that the increased tonus is brought about by the elaboration of a pressor substance somewhere in the body possibly in the ischemic kidney Those who believe that the psychogenic factors are at the root of the disorder are of the opinion that the humoral and neurogenic mechanisms, which are not mutually exclusive are the intermediary means through which emotional conflicts can produce hypertension

There is an increasing body of evidence to support the belief that emotional conflicts may be of primary importance in the development of hypertension Cannon and many other observers have demonstrated that rage and fear in animals and humans are followed by an elevation of blood pressure of a transient nature Longitudinal studies of essential hypertension have shown repeatedly that in the early stages the blood pressure rises and remains elevated *for a transient but variable length of time gradually the basic level* of the blood pressure increases and the transient rises no longer return to the original level It seems probable that in the early and reversible stage the increase in pressure is due to an increased tonus of the arterioles, and as the disease progresses tissue alterations in the walls of the arterioles begin to make the elevation in blood pressure irreversible Psychiatric studies of a number of patients in the early stages of hypertension have demonstrated that there is a direct correlation betwen the periods of emotional tension and elevated pressure and conversely between periods of emotional calm and normal blood pressure In the psychoanalytic treatment of a few cases of early hypertension two patients have been reported as having had their blood pressure return to normal levels apparently permanently and others have evidenced a lowering of blood pressure Since spontaneous remissions of hypertension are not rare it is far too early to evaluate the meaning of this and much more evidence is needed before the psychogenic causation of essential hypertension can be accepted as proved (see page 446)

In studying the psychological aspects of essential hypertension Alexander and his coworkers Saul Weiss and others have demonstrated that there are certain psychodynamic constellations which appear in most patients with this disorder who have been studied Although the number of patients so far investigated by psychoanalytic methods is still too small to warrant conclusions of a general nature the following salient features are reported by Saul

(a) In every case there was a dominant mother with a need by the patient for submissiveness and oral dependence toward her In the male patient this is transferred to the father and there is a resultant hostility and ineffectual rebellion against the need for submission Rage because of the unsatisfied oral demands and because of the need for independent activity cannot be expressed

(b) The hostility developed becomes chronic inhibited and powerful but is not adequately repressed It is near to the surface yet cannot be acted upon nor evaded

(c) Heterosexual activity is inhibited and when indulged in usually gives rise to unrecognized anxiety

(d) Although the conflict between passive dependent wishes and active, destructive hostile wishes occurs in other psychopathological entities it is the *inability of the patient to satisfy either demand consistently which characterizes the hypertensive* He is blocked in both directions and can express neither Satisfaction of either the passive dependent impulses or of the hostile urges leads to a lowering of the blood pressure during the period of such satisfaction

The elucidation of the specific psychodynamic mechanisms related to hypertension will require further investigation and indeed there is as yet no *conclusive proof that any specific psychodynamic mechanism can be directly* correlated with any single physiological reaction in all instances

While the effectiveness of psychotherapy as a means of permanently altering the blood pressure is undetermined at the present time there can be little doubt that some form of psychotherapy is not only desirable but essential in the proper management of essential hypertension In our current civilization almost all people are emotionally disturbed by the mere diagnosis of '*high blood pressure*' *and many of the symptoms which appear during the* course of the disease may be the result of the emotional disturbance rather than the hypertension Furthermore it is probable that these conflicts may even affect the hypertensive process adversely Much can be accomplished by reassurance of the patient by aiding him in solving his current conflicts particularly when they involve hostility by allowing him to give free vent to his hostile thoughts and by allowing him to form a certain amount of dependence upon the therapist Some understanding of the patient s problems and a rather sympathetic permissive attitude on the part of the physician will do much to accomplish these aims in many instances Medical and surgical indications and therapies are considered elsewhere in the book

Hypotension—It is believed by many that a number of cases of so called *hypotension have a large psychological factor present in their illness* This may be of importance etiologically or it may contribute materially to the amount of disability accompanying the disorder Adequate psychiatric studies have not been done up to the present time

GASTROINTESTINAL SYSTEM

Upper Gastrointestinal Tract

Statistical surveys of disorders of the upper gastrointestinal tract made by various observers have indicated that from 25 to 40 per cent of such complaints are *functional in origin* Even though these studies do not take into account the fact that certain so called organic diseases such a peptic ulcer may eventually be proved to be psychogenically initiated the importance of psychological factors is evident That emotional stimuli are involved in the function and dysfunction of the gastrointestinal system should not be an occasion for surprise when consideration is given to two facts (a) the richness of the autonomic nerve supply to the gastrointestinal tract and (b) the

walls increased heart size and others are a result rather than a cause of hypertension There are two major hypotheses as to the origin of this increase in arteriolar tonus The neurogenic theory holds that it is a result of an increased or disordered activity of the vasomotor centers, while the humoral theory considers that the increased tonus is brought about by the elaboration of a pressor substance somewhere in the body, possibly in the ischemic kidney Those who believe that the psychogenic factors are at the root of the disorder are of the opinion that the humoral and neurogenic mechanisms which are not mutually exclusive are the intermediary means through which emotional conflicts can produce hypertension

There is an increasing body of evidence to support the belief that emotional conflicts may be of primary importance in the development of hypertension Cannon and many other observers have demonstrated that rage and fear in animals and humans are followed by an elevation of blood pressure of a transient nature Longitudinal studies of essential hypertension have shown repeatedly that in the early stages the blood pressure rises and remains elevated for a transient but variable length of time gradually the basic level of the blood pressure increases and the transient rises no longer return to the original level It seems probable that in the early and reversible stage the increase in pressure is due to an increased tonus of the arterioles and as the disease progresses tissue alterations in the walls of the arterioles begin to make the elevation in blood pressure irreversible Psychiatric studies of a number of patients in the early stages of hypertension have demonstrated that there is a direct correlation between the periods of emotional tension and elevated pressure and conversely between periods of emotional calm and normal blood pressure In the psychoanalytic treatment of a few cases of early hypertension two patients have been reported as having had their blood pressure return to normal levels apparently permanently, and others have evidenced a lowering of blood pressure Since spontaneous remissions of hypertension are not rare it is far too early to evaluate the meaning of this and much more evidence is needed before the psychogenic causation of essential hypertension can be accepted as proved (see page 446)

In studying the psychological aspects of essential hypertension Alexander and his coworkers Saul Weiss and others have demonstrated that there are certain psychodynamic constellations which appear in most patients with this disorder who have been studied Although the number of patients so far investigated by psychoanalytic methods is still too small to warrant conclusions of a general nature the following salient features are reported by Saul

(a) In every case there was a dominant mother with a need by the patient for submissiveness and oral dependence toward her In the male patient this is transferred to the father and there is a resultant hostility and ineffectual rebellion against the need for submission Rage because of the unsatisfied oral demands and because of the need for independent activity cannot be expressed

(b) The hostility developed becomes chronic inhibited, and powerful, but is not adequately repressed It is near to the surface yet cannot be acted upon nor evaded

Belching.—In the absence of certain organic diseases, excessive belching is almost invariably the result of a neurotic swallowing of air. It is generally used by the patient to reinforce his belief and the belief of others that his symptoms are due to local abdominal pathology rather than to the subjectively less acceptable neurotic conflicts. The symbolic meanings of aerophagia vary with the case.

Indigestion.—The term indigestion is usually used to describe the subjective feelings which accompany lesser dysfunctions of the stomach whether they be of organic or psychogenic origin. Psychologically it rarely if ever has any specific meaning except in so far as it is related to nausea and vomiting.

Anorexia.—Distinction must be made between appetite and hunger although they are usually closely associated and simultaneously stimulated. Either may stimulate the other. Hunger may be thought of as the somatic expression of physiological needs, and appetite as its psychic counterpart. In organic disease the suppression of hunger manifestations usually accounts for the anorexia or loss of appetite. When anorexia occurs without the disappearance of hunger manifestations, although the latter may be suppressed subsequently, the origin of the disturbance is usually psychogenic. When anorexia appears it is usually due to an inability on the part of the individual to accept a conflictual situation and is the symbolic representation of this difficulty. In psychotics it may occur as the result of suicidal drives, and it may express similar wishes in certain neuroses. With rare exception, perversions of appetite are of neurotic or psychotic origin.

A number of studies have indicated that psychological factors may be of importance in disorders of the upper gastrointestinal tract. At the present time some discussion of these factors is warranted for the following conditions: "gastric neurosis," gastritis, peptic ulcer, cardiospasm, chronic cholecystitis and anorexia nervosa. The organic factors related to these conditions and their symptomatology are discussed elsewhere in the book.

Gastric Neurosis.—The term "gastric neurosis" is in reality a misnomer for the symptoms manifested are but a part of the process of a much more widespread and deep-seated neurotic process which affects *not only* the stomach but the whole behavior and function of the individual as well. For psychological reasons the major complaints may be related to the gastrointestinal functions, but any investigation of a more than cursory nature will always reveal that the disorder contains psychopathological phenomena and often other psychophysiological dysfunctions as well. Since the term is a broad one it may be used to delineate a spectrum of conditions ranging from symptoms of a fantasied nature without discernible gastric physiological dysfunction to those conditions of psychogenic origin with measurable physiological alterations. In this latter group are the conditions such as the so-called "dyspepsia" and some of the gastritides of nonorganic origin in which investigation will reveal an actual gastric hyperemia, hyperacidity, or hypermotility of a variable degree of intensity and duration. Local hypofunction may also be found. Thus we see that in this condition of gastric neurosis symptoms may be due to pure psychological formulations or to a combination

powerful associations formed in the mind of the infant between being fed on the one hand and being loved and protected on the other. Everyday life bears constant witness to psychophysiological reflexes such as salivation and gastric activity when thinking of food in a hungry state, and not infrequently one is aware of the hyperacidity accompanying anxiety, the nausea of disgust the slowing of digestion with sorrow and so on. All of these experiences give evidence of the constantly recurring effects of transient emotion upon the functions of the gastrointestinal tract. In extension of this knowledge there are many who believe that chronic emotional disturbance can lead to chronic disturbance of function of the gastrointestinal tract and through this to local tissue alteration.

Most psychiatric studies of the emotional factors related to dysfunction of the gastrointestinal tract have indicated that consciously experienced emotions such as anger, fear, sorrow, and others have only a transient somatic effect and it is generally true that emotional conflicts of a conscious nature can be dissipated by appropriate voluntary activity and so cease to be effective as stimuli producing somatic repercussions. It is the opinion of Alexander and a number of others that the major emotional factors concerned in the upper gastrointestinal disorders are of an unconscious origin, and of these conflicts those related to oral receptive and dependency needs appear to be of primary concern in the majority of cases. These psychodynamic mechanisms will be discussed in greater detail later.

Before the various disease entities are discussed some of the psychological factors related to the major symptoms of upper gastrointestinal disturbance will be presented. Among the symptoms of prominence are pain, nausea, vomiting, belching, anorexia and indigestion.

Pain.—When pain and discomfort are experienced as the result of gastric hypermotility or hyperacidity of psychogenic origin they differ in no way from the pain and discomfort due to hypermotility or hyperacidity of organic origin for the pain producing mechanisms are identical in both cases. When the psychological stimuli are insufficient in intensity or duration to produce a significant local physiological dysfunction the patient usually complains of pain or discomfort which is poorly localized and vague in type. This is commonly seen in so called gastric neurosis and it usually accords with the patient's ideas of what gastric pain should be. On close questioning the pain complained of is often found to be in reality a feeling of tension in the upper abdomen. Except when of delusional origin the pain complained of rarely has any specific psychological connotation.

Nausea and Vomiting.—These symptoms can be considered together in that they are inextricably related in respect to their psychological significance. Almost without exception they represent in a symbolic way an attempt to reject or resist an unpalatable situation which cannot be faced consciously. This is beautifully demonstrated in many cases of hyperemesis gravidarum in which the woman attempts symbolically to rid herself of an unconsciously unacceptable pregnancy and fetus. Globus hystericus is usually found to arise from the same psychodynamic mechanisms as vomiting.

they are of a deeply repressed oral character. Because of the infantile association between these needs and that of hunger and being fed, the frustration of these unrealistic demands for affection and security leads to a chronic reactivation of the psychophysiological responses normally associated with hunger, i.e., the gastric hyperemia, hypersecretion and hypermotility. It is seldom that these oral dependent wishes can be consciously accepted because of the injury to self-esteem entailed and because of the guilt evoked by the primitive demanding aggressive wishes; consequently the individual has usually cloaked these dependency wishes by repression and denial of them. By overcompensation in the form of exaggerated independence he often tends to seek economic security as proof of this self-sufficiency, but when this conscious tangible security is threatened, regression to more primitive dependency needs occurs and the unconscious conflicts are intensified. Thus we usually see the ulcer patient as a hard-working, apparently independent person who will consciously deny and reject any indication of his basic unconscious need of security. Other psychodynamic mechanisms are probably of importance but they have not yet been worked out.

Therapy may be directed towards the local lesion and may be medical or surgical in character. Recently, surgical measures have been directed at the intermediary mechanism, the vagus nerve, with some success, and this procedure tends to confirm the importance of the autonomic nervous system in the genesis of peptic ulcer. Following the removal of symptoms by such a procedure, depression and severe psychoneurotic symptoms have been known to appear, and it must be kept in mind that symptoms often serve the purpose of acting as a safety valve against the development of more seriously disturbing disorders. In a curative sense, deep psychotherapy appears to offer promise but at the present time a sufficient amount of data has not accumulated to warrant conclusions. More superficial psychotherapy can be of immense benefit in many cases, and it involves assisting the patient in solving disturbing reality situations, utilizing transference phenomena to permit the patient to develop a reasonable degree of dependency upon the therapist, thus fulfilling in a limited fashion the patient's unconscious needs, and stimulating the development of activities which with the attainment of an increased proficiency bring an increased sense of security. Except in the hands of a skilled psychotherapist, it is probably wise to avoid therapeutic investigations which lead directly into repressed unconscious material, for if not controlled the emotional reactions liberated may lead to a serious exacerbation of symptoms or to the appearance of disturbing neurotic reactions.

Cardiospasm.—Although there is much disagreement as to the etiology of this condition, current evidence makes it probable that psychological factors are of significance in some cases. Here, as in other gastrointestinal conditions, it would seem that emotional conflicts may act through the vegetative nervous system to produce spasm of the cardiac sphincter, at first transient and then chronic or recurrent. With chronicity the hypertrophy of the sphincter and the atony and enlargement of the esophagus develop as sequelae. The initial episode can often be traced to the occurrence of some traumatic emotional situation which the individual cannot face, and with recurrence of situations

of these plus actual physiological dysfunctions. The mechanisms by which the latter are produced will be discussed briefly under peptic ulcer.

The symptoms of gastric neurosis, which are discussed elsewhere in the book (see page 626), may stem from conflictural mechanisms involving threats to security and dependency wishes and are often accompanied by the affects of anxiety, fear, anger, disgust, or sorrow although the conscious awareness of these feelings may be minimal in some cases. Gastrointestinal complaints may appear as a part of anxiety reactions, hysteria, hypochondriasis or less frequently as delusional manifestations in a psychosis, and again they may or may not be accompanied by actual physiological alterations. If the current psychoanalytic formulations are correct, the central psychological theme in this disorder is the existence of threats against the strong oral needs for affection, dependency and security. Although these psychodynamic mechanisms have been found to be operative in a number of cases, the evidence is insufficient to allow a general application of this thesis at the present time.

Peptic Ulcer.—During the past few decades an increasing amount of direct and subsidiary evidence has made it apparent that emotional factors may be of primary importance in the genesis of peptic ulcer in many patients. A number of studies have indicated that there is a direct relationship between various emotions and the motor, vascular and secretory activity of the stomach in man and in animals. The classic studies of Wolff and Wolf in a patient whose persistent gastrostomy permitted continuous visualization of the gastric mucosa clearly demonstrated that specific mucosal, secretory, and motor changes regularly accompanied certain emotional states. For example in situations which engendered anxiety there was a marked degree of hyperemia, hyperacidity and hypermotility which persisted as long as the threat of loss of job which led to the anxiety. Even more importantly it was noted that during such states of mucosal hyperactivity the tendency towards petechial hemorrhage and ulceration was greatly increased and the ulceration tended to persist. Thus it was established that an abnormal status of the gastric mucosa of psychogenic origin predisposed to the formation and persistence of ulceration.

The hypothesis of the exponents of psychogenic causation in peptic ulcer may be summarized briefly as follows. Certain emotional conflicts in some individuals may stimulate the autonomic nerves of the stomach in a specific fashion and thus produce alterations in the gastric motility, secretions and vascularity which predispose to ulceration. The ulceration may be brought about by chemical, thermal or mechanical irritants but it is the abnormal state of the mucosa which makes the ulcer slow to heal and this abnormal mucosal condition will persist as long as the initiating emotional conflicts remain active. Alexander, his coworkers and others believe that there may be specific psychodynamic constellations related to the gastric dysfunction which predisposes to peptic ulcer and the psychoanalytic material uncovered thus far tends to bear out their assumptions. In summary, the conflicts common to the patients they have studied are as follows. There are powerful unconscious wishes to be fed, loved and cared for, usually by the mother. These demands may be of a passive receptive or aggressive demanding nature and

strated that alterations in colonic function such as changes in tonus and peristalsis mucosal engorgement and blanching increased or decreased secretion of mucus and lysozyme and mucosal petechial hemorrhages may all appear as a result of emotional stimulation As in disorders of the upper gastro intestinal tract, it is assumed by an increasing number of physicians that while transient colonic dysfunction is produced by acute emotional disturbances chronic emotional conflicts may lead to chronic dysfunction and through this may produce local tissue alteration in the colon of certain individuals In the succeeding discussions disorders of the colon due to known organic diseases such as carcinoma typhoid fever, poisons parasites etc will be excluded

In disorders of the colon four symptoms are of major importance pain hemorrhage diarrhea and constipation Psychological factors usually are of importance only in the latter two

Diarrhea — As mentioned above transient frequency of bowel movement or diarrhea may be produced by emotional stress If such manifestations are transient they are not of importance although when the psychological stimulus is minor it is usually found that those individuals who develop diarrhea have an unstable emotional background When diarrhea of this type occurs it is probable that an increased colonic peristalsis as a result of autonomic stimuli of psychogenic origin is responsible In the absence of a responsible organic condition chronic diarrhea of psychogenic origin is known to occur and it is usual to find that the related emotional conflicts are deeply buried in the unconscious and are of a primitive nature In a psychoanalytic sense these conflicts are concerned in some cases with a need for giving in a symbolic way as a restitution for symbolic oral taking of a hostile nature Psychological regression to the anal phase of development is involved

Constipation —In the absence of organic causation this extremely common condition is perhaps best regarded as a symptom rather than as a specific disease entity While there may be a certain value from the standpoint of chemotherapy in dividing constipation into spastic atonic and dyschezic types it is doubtful that such categorization has any etiological significance It is often stated that neurogenic and habit mechanisms are responsible for the colonic variations and it is probable that this is true However this explanation does not seem to go far enough in the majority of cases for it leaves the origin of the autonomic dysfunction and of the habits unexplained It is probable that in many instances neurotic conflicts can be found at the root of the autonomic imbalance and the improper bowel habits Psychoanalytic studies of some cases have demonstrated that in part it may be due to a desire to withhold a symbolically valuable part of the body and that the process of retention may be related to a primitive sexual urge of an anal character It is known that primitive anal regressive mechanisms play an integral role in most paranoid psychoses and it is interesting to note that 72 per cent of such partial confirmation of psychoanalytic ideas about constipation cases had constipation whereas constipation was found in only 26 per cent of a control group

which impinge upon the basic conflicts there is a recurrence of the spasm. While sufficient data are not yet forthcoming, it appears probable that the basic psychodynamic problems are based upon conflicts of an oral nature, and that they are situations which in a symbolic sense the patient cannot "swallow." It is probable that psychotherapy would be of real benefit in the treatment of this condition, particularly in the early stages. This may be carried out in conjunction with such measures as mechanical dilatation in the later stages of the disease.

Anorexia Nervosa.—All of the physical symptoms and signs exhibited in this interesting disease can be explained on the basis of the undernutrition which characterizes it. In the absence of primary organic disease such as destruction of the pituitary gland, it is probable that the lack of appetite and the avoidance of food which lead to the inanition are due to psychological factors. Severe psychoneurotic and even psychotic processes are invariably present in such individuals. The emotional conflicts involved in this disorder are varied. Not infrequently there are unconscious fears of oral impregnation, marked inhibition of heterosexuality, or ideas in which obesity and pregnancy are equated. Because of fears of sexuality and pregnancy and the unconscious relationship of such activities with normal or obese body configuration, the patient starves herself to prevent the possibility of such happenings occurring to her. At times powerful unconscious hostility leads to marked guilt reactions, and suicidal impulses in the unconscious lead to starvation as a means of attaining this goal. In certain schizophrenics the attempt to withdraw from reality leads to the avoidance of food along with other manifestations of reality. In conditions with severe oral conflicts not unlike schizophrenia there may be a failure in ego development, and anorexia nervosa may occur during periods of emotional stress, particularly when dependency relations to the parent are threatened. In all of these conditions it is probable that the starvation creates some endocrine dysfunction and this in turn increases the loss of appetite. Psychotherapy in conjunction with attempts to maintain nutrition is the only measure which offers prospect of success in this condition, and because of the severity of the psychiatric disturbance psychotherapy is often difficult.

Chronic Cholecystitis.—Although there is evidence to the effect that psychic factors may markedly increase or decrease the rate of flow of secretions from the biliary tract, the psychological factors related to cholecystitis have not been adequately studied. Wittkower has demonstrated that annoyance produced cessation of biliary flow in the patients he studied, and clinicians have noted that there is a high incidence of emotional situations which produced annoyance just preceding the first two or three attacks of biliary colic in a large series of cases. This relatively virgin field is in urgent need of exploration.

Lower Gastrointestinal Tract

It has been common knowledge for centuries that frequent bowel movements or diarrhea may be the result of certain emotional stimuli such as anxiety or fear. Less well known is the fact that constipation may also be of psychogenic origin. Experimental and clinical investigation has demon-

tion increased lysozyme production or other enzymatic reactions While all of this has not been proved a number of clinical and experimental observations make it probable that this or a very similar chain of events occurs in the development of ulcerative colitis

The studies of Murray Lindemann Groen Ross and others on the personality structure of patients with ulcerative colitis indicate that with minor variations there is essential agreement on the basic psychological structure of most cases All of the patients give evidence of profound psychoneurotic mechanisms with psychotic characteristics not far from the surface in a number of them Hysterical depressive and compulsive reactions are predominant and manifestations of the anal phase of development such as rigidity overtardiness and masked hostility are prevalent While these patients are superficially pleasant and cooperative as a rule powerful hostility and marked overdependence upon some central figure are almost invariably found under this apparently unperturbed surface In from 50 to 75 per cent of the cases the onset of exacerbation of the disorder follows closely upon the loss of the loved person either through estrangement, departure or death This breach of dependency relationship is of the utmost importance in these individuals not only from the standpoint of dynamics but also from the fact that *successful psychotherapy must be based upon it*

Numerous medical and surgical remedies have been used in the treatment of ulcerative colitis with indifferent success It is becoming increasingly evident that psychotherapy must be an integral part of the management of these patients if success is to be attained The essential point in psychotherapy is the establishment of a strong transference relationship to the therapist so that he may replace the lost love object upon whom the patient has been so profoundly dependent This is best accomplished not by verbal exploratory psychotherapy but by a sympathetic noncritical support of the patient in which the therapist takes the role of a firm kindly parent and assists the patient with his problems To this end all supportive measures such as sympathy reassurance massage warm baths simple feeding routines and symptomatic medication may be desirable Gradually after the acute manifestations have subsided a slow re education of the patient towards dependency upon some more normally related person may be attempted Psychotherapy of the verbal type must be kept to a minimum during the acute phases of the disease and it must be limited to material which the patient uncovers voluntarily even then the brakes must be kept on and at the slightest sign of increase in somatic symptoms it must be terminated *The only reliable guide to therapy is the increase or decrease in somatic symptoms* Even during the quiescent stages of ulcerative colitis verbal exploration of unconscious conflictual material must be undertaken with the utmost of caution Injudicious exploration can only lead to an exacerbation of symptoms and even death or it may replace the somatic manifestations by an even more disabling psychoses It is characteristic of these patients that the somatic disorder often exists as an alternative to a psychosis and this dilemma may also exist in some of the other more serious psychosomatic disorders such as arthritis hypertension peptic ulcer anorexia nervosa obesity asthma and others The efficacy of

Of the various disorders of the lower gastrointestinal tract the psychological factors will be discussed briefly in Mucous Colitis and Ulcerative Colitis

Mucous Colitis—The investigations of White Cobb and Jones, Bockus Bank and Wilkinson Alexander and others have indicated almost beyond question that the manifestations of mucous colitis are the result of the effects of an overactive parasympathetic system upon the motor and secretory mechanisms of the colon They further indicate that it is highly probable that the overstimulation of the parasympathetic nerve supply to the colon is psychogenic in origin Their studies show that there is a high incidence of neurotic manifestations in those patients with this affliction and that for the most part the neuroticism antedates the disease that emotional traumata often preceded recurrences or exacerbations and the patients were often aware of this connection Phobic compulsive and depressive symptoms were among the most common neurotic manifestations noted Alexander and his coworkers after careful psychoanalytic study of a small group of cases came to the conclusion that they could be divided into two main psychological groups the colitis group and the constipation group The essential psychodynamic features of these two groups are given in part under the discussions of the symptoms Diarrhea' and Constipation" It is probable that many cases of mucous colitis have unconscious conflicts which are closely related to those described by Alexander For elaboration of these concepts the reader is referred to the original articles

Although symptomatic measures may be necessary in the treatment of this disorder the major reliance should be placed on psychotherapy In the more chronic and severe cases deep psychotherapy may be required but in others more superficial psychotherapeutic procedures are often of considerable value These should include explanation in simple terms of the emotional origin of the disorder advice in the solution of the known conflicts and measures directed towards strengthening the defenses of the individual A sympathetic noncritical attitude which permits the patient to discuss freely his worries and fears may be of immense value

Ulcerative Colitis—Ulcerative colitis is another disorder in which the profound organic changes tend to make the physician skeptical of the possibility of psychological factors being important in the etiology While it is not here contended that emotional disturbances are the sole source of pathology the psychiatric and psychologic data which have accumulated strongly suggest that emotional factors are of real importance if not essential to the development and continuation of ulcerative colitis The hypothetical means by which this is believed to come about is in summary as follows Disturbing emotional traumata of a relatively specific sort act to intensify unconscious conflicts in these individuals This emotional stimulus activates the autonomic nervous system to produce the boggy hyperemic hypersecretory mucosa and the oversensitive hypermotile colon Upon this morbid base petechial hemorrhages in the mucosa either spontaneous in origin or from minute mechanical traumata, become ulcerated and the ulcers do not heal in certain individuals because of undetermined factors which may include specific or nonspecific infec

following factors to be of significance The patients had a remarkably close psychological dependence upon a parent, lover, or child and tended to bind them by a smothering affection and overdependence a schism in this relationship was often related to the onset of the disorder and without repeated evidence of their importance to others the patients were inclined to feel helpless and hopeless It is probable that these factors are not enough in themselves to produce the hyperthyroidism factors such as organic predisposition may be involved as well Certainly further investigation of the psychophysiological relationships in hyperthyroidism is needed before dogmatic assertions as to etiology can be made However, the findings are sufficient to warrant the need for a thorough investigation of the psychological status of each hyperthyroid patient Evidence already exists to indicate that psychotherapy may be of real benefit to many patients with hyperthyroidism and in some of these individuals particularly the relatively nontoxic ones the toxicity has disappeared and the basal metabolic rate has returned to normal with no other treatment than psychotherapy

The symptoms of hypothyroidism may be closely simulated by neurotic manifestations and this is particularly true of those patients whose basal metabolic rate is on the border line of normal Psychoneurosis should always be thought of as a possible cause for symptoms in the lesser degrees of hypothyroidism whether or not there is a related depression of thyroid function in some of these patients has not been sufficiently studied

Islands of Langerhans—The regularity with which hyperglycemia accompanies certain emotional states such as fear and rage makes it apparent that psychological factors are closely related to the function of the glucose regulating mechanisms of the body While this altered glycemic state is known to be due in part to the secretion of adrenalin there is evidence to *indicate that the insulin producing mechanisms are involved as well* In spite of the fact that this information has been available for some years relatively little attention has been paid to the possible relationship of psychological factors to diabetes mellitus W C Menninger who undertook a psychiatric evaluation of a small group of diabetic patients was able to demonstrate that the course of the glycemia and glycosuria paralleled the mental status and that with emotional recovery the diabetic condition cleared up insulin and dietary therapy no longer being required Although the factors of long continued anxiety and fatigue passive personality tendencies and depression may be of importance in relation to diabetes, there is little information about psychological constellations which bear any specific relation to diabetes It is probable that emotional conflicts lie at the root of the dietary indiscretions and the mismanagement of insulin which so disturb the regime of certain diabetic patients Psychotherapy may be of material assistance in solving this problem

Recently evidence has appeared which suggests that there is a direct relationship between hypoglycemic states and neurotic conflicts in some individuals More investigation will be needed in the psychosomatic mechanics of diabetes and hypoglycemic states before a clear understanding can be obtained

psychoanalysis in the treatment of ulcerative colitis has not yet been properly assessed although preliminary reports are encouraging Even with psychoanalysis it is evident that it would be unwise to begin such therapy during the acute stages of the disease, and therapy must be governed by somatic symptoms at all times

Chronic Appendicitis —While adequate psychological studies of this condition have not been made it is evident to the most casual observer that many an innocent appendix has disappeared under the knife for symptoms which were entirely neurotic in order or derived from minor psychogenic disturbances of the colon

ENDOCRINE SYSTEM AND METABOLISM

The endocrine system and metabolism occupy an unusual role in the field of psychosomatic medicine for not only are the various glands subject to disorders of a specific nature but often they are also the intermediary mechanism between emotional disturbances on the one hand and dysfunction of special organs or organ systems on the other Moreover, the functions of the various glands are so closely integrated and interrelated that a malfunction of one gland is often reflected in the disharmony of others and in an alteration in general metabolic efficiency It is beyond the scope of this book to discuss the intricate interfunctioning of the neurohumoral systems and the emotions Fenichel has aptly described this as ' the disturbed chemistry of the unsatisfied person ' and there is little doubt about the fact that emotional stimuli can and do affect endocrine function

Every physician is familiar with the hypersecretion of adrenalin with fear and anger and the delayed menstruation of the woman in fear of pregnancy is common knowledge In many articles on hyperthyroidism emotional trauma is mentioned as a precipitating factor and in certain patients the onset of diabetes has been attributed to emotional stress It is probable that psychogenic stimulation of the gland through the autonomic system is the activating mechanism in some of these reactions and it is reasonable to assume that the various tropic hormones of the pituitary gland secreted under the influence of the emotionally stimulated hypothalamus may be the responsible factor in other instances In the following discussions we shall concern ourselves only with the psychological factors believed to be related to specific endocrine glands and metabolic disorders Dysfunction of primary organic origin will be omitted and only a few of the major diseases will be discussed

Thyroid Gland —As previously mentioned emotional factors are referred to as a possible precipitant in hyperthyroidism but in the majority of these studies 'emotional factors are used in a loose sense of the words and no adequate psychodynamic investigation has been undertaken In those reports whose orientation was psychiatric the facts uncovered made it probable that psychological reactions were closely related to the appearance of the hyperthyroidism and may possibly be of etiological significance in the disorder Conrad in a study of 200 men and women with hyperthyroidism, found a history of apparently significant psychic trauma in 94 per cent of the cases Lidz, whose findings are in agreement with Conrad s, believes the

up the gratification of eating frequently or large amounts The complaint of irritability during the process of reducing is not uncommon and it is due probably to frustration of the emotional need to eat rather than to physiological reactions One of the first aims in the treatment of obesity is to make the patient aware of the amount and frequency of eating Awareness of the substitution of eating for other desired pleasurable activity is also a desirable goal Psychotherapy is the only reliable means by which these ends can be attained

LOCOMOTOR SYSTEM

The reactions of the voluntary musculature to emotionally charged situations are a matter of almost daily observation The play of expression upon the face in sorrow joy anger and apprehension and so on are so routinely seen as to all but escape conscious realization Less obvious but equally common are the bodily postures accompanying various emotions and psychogenic alterations in muscular tonus are a matter of experimental record From the standpoint of pathology it is probable that the muscular "set" which accompanies fear and hostility is the most important In the long development of evolution it has been essential for the survival of the individual that he be in a state of instant readiness to act either by fighting fleeing or protective immobilization at the first warning of a threatening situation This propensity for muscular preparedness has persisted to the present day and recent psychological investigations have shown that these reactions can be evoked by emotional threats as well as by physical dangers It is the concept of many psychiatrists that when these phantasied threats are chronic and unconscious they may be a persistent stimulus which produces a varying but continuous alteration in muscle tone It is possible that this continuous increase in tonus may lead to pain and dysfunction and may be an integral part of the process which ends in arthritic changes While there is strong evidence that psychogenic factors are of importance in that rather vague group of disorders which are combined under the lay term of rheumatism convincing demonstration of the role of emotional conflicts in arthritis is not yet forthcoming Nevertheless it has been demonstrated by Johnson and others that there are striking similarities in the personality structure of patients suffering from rheumatoid arthritis The essence of these findings is that when the patient cannot discharge hostility by competing with or being of service to others the inhibited aggression finds outlet of an ineffective type in altered muscular tension and in arthritic reactions The hostile state is believed to be a reaction to an early masochistic dependence upon the mother which is carried over into all human relationships It is possible that the adrenal cortex may be involved as an intermediary agent in arthritis (See discussion of the adrenal cortex) None of these hypotheses contends that psychogenic factors are the sole origin of arthritis but psychotherapy has alleviated the symptoms and decreased the disability in a few cases In short these is reason to believe that emotional factors may be of importance in rheumatoid arthritis and in related conditions

Adrenal Cortex—It is well established that the adrenal cortex or its secretions are intimately related to the metabolism of glucose and nitrogen among other things Selye and others have shown that the cortex is implicated in an important way in the response of the organism to stress whether it be of a physical or emotional nature This he terms the "Adaptation Syndrome" and there is in the experimental evidence some suggestion that pathological conditions which are not dissimilar to disorders such as periarteritis nodosa rheumatoid arthritis certain lymphadenopathies and other disorders may represent the end result of a pathological adaptation to physical or psychological stresses Whether or not this hypothesis is eventually proved to be true, there is little doubt that the response of the adrenal cortex to stress may be of profound importance in a number of psychosomatic conditions

Little is known about the relationship of emotional factors to diseases of the adrenal cortex but it is well known that symptoms of lassitude fatigue and weakness are often attributed to cortical dysfunction when they are in reality manifestations of a psychoneurosis

Other Glands—While impotence and other disorders of a sexual nature are often attributed to hypofunction of the gonads, it is seldom that this is found to be true By far the greater part of such problems lie entirely within the realm of psychiatry and for proper therapy it is mandatory that every patient with such complaints be given a thorough psychiatric evaluation Dysmenorrhea has been found to be closely related to emotional conflicts usually basically sexual in nature in many individuals and there is strong evidence that psychological considerations may be of real importance in other gynecological conditions such as leucorrhea In all of these genital and sexual disorders the emotional factors may be of importance not only from the viewpoint of etiology but also from the standpoint of complications and sequelae

Obesity—One of the commonest ills of present day civilization is that of obesity It is usual for the individual so afflicted to protest that it must be glands I scarcely eat a thing In truth obesity is rarely glandular although after the climacteric endocrine alterations may be concerned in the site of deposition of the fat Obesity is determined by one mathematical and inexorable rule if the calorie intake exceeds the calorie output then weight is gained

It has been found that the usual reason for excessive eating is almost invariably psychological Eating is not only a reactivation of the primitive oral pleasure but also food may often be the symbolic equivalent of affection Thus many individuals who find other sources of pleasure such as sex or affection denied them unconsciously turn to the more *infantile* gratification of eating as a pleasurable activity In many obese women it has been demonstrated that the protuberant abdomen is a symbolic substitute for a desired pregnancy in others femininity and pregnancy is feared and obesity serves the purpose of making them less attractive and thus in less danger of heterosexuality

The treatment of obesity is often troublesome because while the patient wishes to lose weight he is at the same time unconsciously unwilling to give

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Conversion hysteria may produce many bizarre muscular phenomena such as spasticity paralysis, paresis, spasmodic movement, and so on Descriptions of these reactions will be found in many psychiatric texts and articles

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CHAPTER XVII

DISEASES OF THE LOCOMOTOR SYSTEM

INTRODUCTION

Diseases of the locomotor system include all conditions which interfere with the proper function of the muscles bones joints and ligaments, or periarticular tissues In addition to these structures many neurogenic conditions may interfere with bodily movement these have been considered under Diseases of the Nervous System It is seldom that the locomotor system is the site of a local disease One of few exceptions to this is osteogenic tumors In general practically all the lesions of muscles bones and joints are dependent upon some systemic or neurogenic disturbance Many examples might be cited such as the arthritis in rheumatic fever and gonorrheal bacteriemia the bone lesions of scurvy and rickets due to avitaminosis osteofibrosa cystica resulting from hyperparathyroid function and muscular wasting as found in scurvy, peripheral nerve lesions and chronic debilitating diseases Therefore many of the important conditions which interfere with locomotion are dealt with in other sections. Although the majority of these lesions are obvious as to their character the fundamental cause is often unknown It is seldom that one tissue alone is affected, as for instance in a chronic arthritis not only are the periarticular and articular structures affected but there are also found changes in the bones and muscles Therefore in considering any individual case the symptoms and signs must all be carefully analyzed in relation to the probable primary cause

DISEASES OF THE BONES

Diseases of the bones may be classified under three main headings namely new growths infections and metabolic disturbances The first are usually dealt with as surgical diseases in that their therapy principally lies in this field The infections are mainly encountered in tuberculosis syphilis, typhoid fever and pyogenic infections The osseous tissues proper the medulla or the periosteum may be involved individually or collectively producing an osteitis periosteitis or osteomyelitis

Tumors

The following classification of tumors of the bones has been recommended by the American College of Surgeons

I Tumors related to cartilaginous growth
  1 Bone cysts or osteitis fibrosa.
     A. Solitary, B multiple.
  2 Benign giant cell tumor
     A Typical B variants of giant cell tumor
  3 Osteolytic sarcoma
     A Chondroblastic B osteolytic forms of osteogenic sarcoma

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In addition to the osseous lesions there are a number of systemic features which indicate that the disease is not a local one Bronchitis and emphysema are common and may be explained by the changes in the thoracic cage, also numerous neurologic symptoms and signs such as paralyses, the pain and other sensory disturbances are due to the involvement of the spine In about 65 per cent of the cases Bence Jones protein is found in the urine This is a protein with a small molecule and readily passes through the healthy glomerular membrane It is recognized on heating acidulated urine to 60 C, when a flocculent coagulum appears only to fade away as the temperature approaches to the boiling point On cooling the cloudiness reappears but again clarifies as about 40 C is reached In these cases it is customary to



Fig 4 0—X ay f the skull n a case f multiple myeloma. Note the haracteri t c appearance of nu erou mall pur hed out a ea C mpare w th F g 444

find an increased amount of nonprotein nitrogen in the blood This is not due to urea uric acid or creatinine nor are there other signs of impairment of renal function The power of urinary concentration is maintained and the arterial blood pressure is low The exact cause of this nonprotein nitrogen retention is at present unknown Examination of the blood reveals no abnormalities unless there be anemia, which distinguishes it from *Chloroma*' (see page 560) Severe secondary anemia lowered plasma proteins edema and emaciation occur in advanced cases

The x ray findings suggest the true nature of the lesion There will be found varying numbers of round or oval punched areas resembling small cysts in the bones mentioned above (see Figs 430 and 431)

II Tumors related to precartilaginous and preosseous connective tissue
  1 Benign osteochondromas or exostoses
    A Single, B multiple
  2 Central chondromas or chondromyxomas
  3 Osteogenic sarcomas containing cartilage or chondromyxosarcoma
    A Primary, B secondary
  4 Osteogenic sarcoma with osteoblasts

III Tumors not primarily of osseous origin
  1 Ewing's endothelial myeloma
  2 Multiple myeloma
  3 Metastatic carcinoma
  4 Fibrosarcoma.

For a description and discussion of tumors of the bone the reader is referred to textbooks on the practice of surgery It has been the custom to deal with them in such texts much more fully than in books devoted primarily to medicine Whether this is altogether advisable is open to argument The principal excuse for this custom seems to be in the fact that the majority of the lesions are local and cannot, therefore, be considered as systemic disturbances and, further, they are usually amenable to surgical therapy There are however, several osseous conditions that can with propriety be considered at this juncture

Multiple Myeloma

Synonym —Kahler's disease

Definition —Multiple myeloma is a systemic disease of the bone marrow consisting of sharply defined tumors which replace the medullary tissues and sometimes invade the compact bone

Etiology —The cause of this disease is not known It is not found in the early decades but occurs with increasing frequency after thirty and reaches a maximum incidence between fifty and sixty

Pathological Anatomy —There is much evidence to suggest that the tumorlike masses arise from a bone marrow element which is not concerned with blood formation The process begins in the medulla and through invasion of the compact bone reduces this to a mere shell which is easily broken The contents of these masses appear to be a mixture of leucocyte cells erythrocytes and fat in a jelly like condition The most common sites for the lesion are the spine ribs cranium and the proximal ends of the femora and humera

Symptoms and Signs —The initial symptom in the majority of cases is intermittent rheumatic pain felt in a variety of places determined by the position of the lesion It usually radiates to the arms and legs and may have girdle distribution The onset is insidious and is aggravated by movement There are violent exacerbations and blessed remissions but the progress is to an agonizing termination The most severe pain is undoubtedly due to pressure on the spinal roots and the remissions result from tumor regression

There is skeletal deformity in 60 per cent of the cases from bone destruction leading to sinking of the sternum kyphosis and pathological fractures which are most frequent in the ribs

Prognosis—The course is uniformly to a fatal termination in about six to twelve months although patients have been reported who have lived for five years

Treatment—There is no known specific therapy As far as possible pathologic fractures should be prevented and when they do occur it must be appreciated that they heal if properly treated and fixation in good position is usually sufficient Surgical interference for the correction of pressure complications such as laminectomy for paraplegia is indicated as a temporary measure

Chloroma

See page 560 under Acute Leucemia

Osteitis Fibrosa Cystica

See page 964 under Hyperparathyroidism

Metastatic Carcinoma

Metastatic carcinoma of the bones presents an extremely variable group of symptoms "Rheumatic" pain is the outstanding symptom This may be localized when a single focus is present (50 per cent) which is usually in the end of one of the long bones at the site of the entrance of the nutrient vessel *On the other hand they may be without number when the pain will be diffuse* and its multiplicity makes it impossible of accurate location Under the latter conditions there is usually an increased oxygen consumption and Bence Jones protein may be found in the urine (see page 1206)

The principal sources of bone metastases are primary carcinoma of the prostate breast thyroid and hypernephroma which account for over 75 per cent They may arise however from many other sources

Metabolic and Developmental Disorders

Many of the pathological conditions of the bones due to metabolic and developmental disorders have already been referred to in diseases of nutrition ductless glands and the reticulo endothelial system A summary of these disorders will be found as follows

Avitaminosis
- Rickets (page 99)
- Renal rickets (page 1?81)
- Osteomalacia (pregnancy) (page 803)
- Scurvy (page 95)

Hyperparathyroid Function
- Osteitis fibrosa cystica (page 964)

Pituitary Function
- Acromegaly (page 893)
- Gigantism (page 89)
- Dwarfism (page 906)
- Pituitary basophilism (page 896)

Diagnosis.—The diagnosis rests upon the x-ray findings and the presence of Bence Jones protein in the urine. It is to be distinguished from metastatic carcinoma in the skeleton. At times this may be impossible without a biopsy as in both conditions the x-rays may be identical and Bence Jones protein may be present. A primary tumor and metastases in the lung (rare in myeloma) are in favor of carcinomatosis as is also a single tumor. But only



Fig. 431.—X-ray of the humerus and shoulder girdle in a case of multiple myeloma. Note the characteristic punched out area particularly in the humerus and ribs. Compare with *Figs.* 366 and 445.

a single area may be found in myeloma and multiple bone metastases are found in carcinomatosis. An increased oxygen consumption (B.M.R.) is in favor of the latter.

Other conditions to be distinguished from myeloma are chloroma (page 560), osteitis fibrosa cystica (page 964) and osteitis deformans (page 1222). A thorough examination readily reveals the true diagnosis.

is flattened, the lower jaw is prominent, and the tongue and lips are thickened There is a real as well as an apparent enlargement of the head The trunk is normal in size and proportion while the extremities although well formed are short *which is particularly apparent in the legs Instead of the center of* the stature being at the symphysis pubis it is nearer the xiphoid (Fig 432)

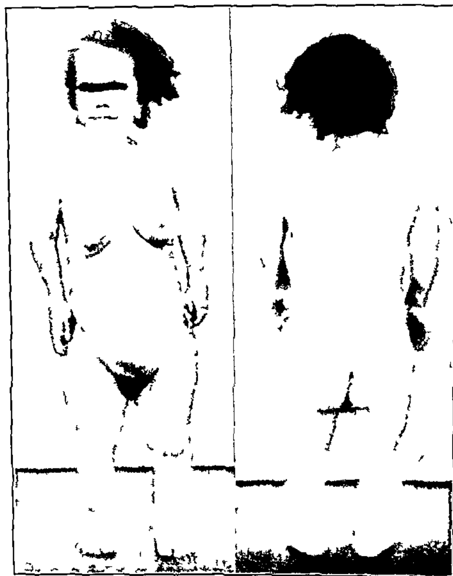


Fig 432 Fig 433

Fig 432 —Front view photograph of a female with achondroplasia aged thirty seven eight and a half months pregnant
Fig 433 —Rear view photograph of the *same patient as shown in Fig 432*

The hands are small and the fingers tapering all of them being of about equal length and when extended appear like the spokes of a wheel known as the main en trident The muscles of the extremities appear to be hypertrophied or abnormally developed but their physical strength is not increased The skin

The diseases of the bones that have not been dealt with elsewhere are principally confined to those that have a hereditary or unknown background and most of these come under the former category In fact it is one of the interesting observations in clinical medicine that it is not unusual for a familial or constitutional direction to be given to many of the diseases of the bones, joints and muscles They do not, however, follow the general rules of inherited characteristics but are more inclined toward a scattered accidental occurrence The more important of these diseases are achondroplasia, hereditary deforming chondrodysplasia, osteogenesis imperfecta, and with a suggestive familial tendency, osteitis deformans

Achondroplasia

Synonym —Chondrodystrophia fetalis

Definition —Achondroplasia is a form of dwarfism due to arrested development of the long bones of the extremities resulting from a perversion of normal endochondral ossification There have been three forms described chondrodystrophia malacia in which the lesion is a softening of the epiphyseal cartilages, chondrodystrophia hypoplastica, where there is an abortive cartilaginous growth and chondrodystrophia hyperplastica, where the epiphyseal cartilage overgrows and leads to outward enlargement

Etiology —Congenital and hereditary factors play a dominant role in the causation of this disease A number of achondroplastic dwarfs may be found in one family, being more common in males than in females It has been attributed to an abnormally small amnion leading to increased hydrostatic pressure which is supposed to cause a dystrophy of the original bone cartilage Another suggestion has been that it is related to cretinism, but both these theories at the best must be considered as speculative

Symptoms —The majority of achondroplastics are stillborn having developed to a fetus between the seventh and ninth months The death rate of those that come to term is high in the first six months of life, but after this time they do not show any abnormal impairment of their general health Skeletal abnormalities at birth remain unaltered The infant is short, usually about three fifths to four fifths the normal length the bridge of the nose

is thickened over the whole body, and about the joints it may appear in folds as if it were too long for the shortened bones Mentally they are quite alert and both sexes are likely to exhibit increased sexual capacity and the females are expected to be prolific

The x rays of the limbs are unique, the long bones being shortened thickened and dense *The line of ossification is irregular and defective* The epiphyses show a sudden expansion as compared to the shafts (Fig 434) There is a type of achondroplasia in which the shafts of the bones appear softer than normal and as a consequence may undergo considerable distortion An example of such is seen in Fig 435

Pathological Anatomy—The anatomical changes appear to be the findings expected from the x rays The epiphyses are hypertrophied and the shafts of the bones show active periosteal proliferation, while the endochondral ossification is absent There is, however a complete aplasia of the long bone development while the epiphyses are abnormally enlarged

Diagnosis—The diagnosis is made without difficulty as there is no other disease which simulates its peculiar characteristics

Treatment—*There is no known treatment*

Multiple Cartilaginous Exostoses

Synonym—Hereditary deforming chondrodysplasia

Definition—Multiple cartilaginous exostoses is a condition where numerous exostoses of congenital origin occur chiefly toward the ends of the long bones

Etiology—This condition may occur in members of the family of the same generation and in different generations but it does not follow the Mendelian laws They are supposed to be due to a developmental anomaly of the epiphyseal cartilage and by others are considered as misplaced cartilaginous tissue which in time forms true bone

Symptoms—There are no objective or subjective symptoms unless they interfere with local function The exostoses are usually recognized on palpation or by x ray examination They are always multiple and may number scores even to more than one hundred and are most commonly found at the ends of the long bones the ribs vertebrae and pelvis If they occur in the legs or forearms the bone principally affected does not grow as much as its companion and therefore a deformity may develop The x ray pictures show the position and shape of the exostoses and also demonstrate that it communicates directly with the medullary cavity (see Fig 436)

Pathological Anatomy—The outer surface of the exostoses is formed by perichondrium beneath which is cartilage and within this sheath cancellous bone may be found Occasionally sarcomatous changes occur The other unusual features are accidental such as fractures pressure on nerve trunks or even on the spinal cord when the vertebrae are involved erosion of blood vessels producing aneurysms etc

Diagnosis—This is made with certainty by x ray examination

Treatment—If they cause pain from pressure or interfere with function they should be removed by surgical methods

Fig 434 —X ray of the legs in a case of achondroplasia



Fig 435 —X ray of the arm in a case of achondroplasia.

Pathological Anatomy —The anatomical change is found at the junction of the diaphysis with the metaphysis where a protruding mass of hyaline cartilage is found

Diagnosis —When the condition is multiple, there is little difficulty in recognizing its true condition, but if single it may be confused with fibrocystic diseases chondroma a giant cell tumor or other local bone lesion

Prognosis —It does not affect the general health and is only of importance when the tumors interfere with skeletal function

Treatment —There is no treatment known which affects the general course of the disease If the tumors interfere with function they should be removed



Fig 43 —X ray of a hand in a case showing multiple congenital enchondromas (From the Children Memorial Hospital Montreal)

Osteogenesis Imperfecta

Synonyms —Fragilis ossificans, osteopathyrosis fragilitas ossium Lobstein s disease

Definition —This is a rare disease of the bones which is characterized by great fragility and numerous fractures usually recognized in infancy and childhood

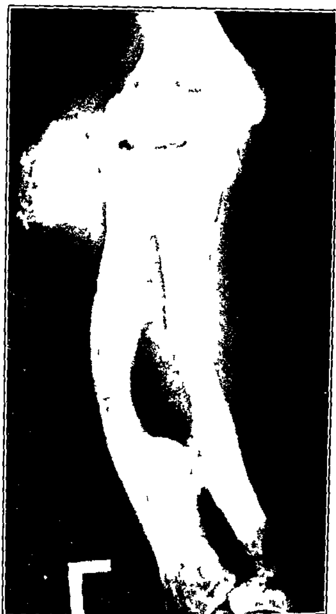


Fig 436 — X ray of the left fore arm in a case of multiple cartilaginous exostosis (From the Montreal Neurological Institute)

Multiple Congenital Enchondroses

Synonyms —Dyschondroplasia, multiple enchondromata

Definition —There is an abnormal growth of bone and cartilage in the growing end of a bone which may be either single or multiple

Etiology —It is a rare congenital disease of unknown cause, but appears to be due to a congenital abnormality of the epiphyseal cartilage

Symptoms —This lesion is irregularly distributed but is most frequently found in the phalangeal and metacarpal bones The next most frequent site is the long bones of the extremities It is recognized either by a palpable mass or through localized lack of development The x ray pictures reveal what appear to be cartilaginous protrusions or masses which contain irregular areas of calcification (see Fig 437)

tures The bone shadow is extremely thin and often can hardly be distinguished from the surrounding soft parts This is accentuated by the increased density where fractures have occurred The medullary cavity when seen is irregular and dilated the epiphyseal line is straight and the cartilage thin With such profound changes in the structure of the bones it would be expected that definite changes in the metabolism of calcium phosphorus magnesium or potassium would be detected but the results so far reported are conflicting In fact the results have been within normal limits in the more carefully conducted observations except perhaps for a slight negative calcium balance The long bones are principally affected as represented by the number of fractures but fractures of the bones of the skull have also been reported

Pathological Anatomy—The anatomical changes consist of an extreme fragility due to thinning particularly of the shafts of the long bones and ribs The epiphyses are normal and there is no increased flexibility of the bones the whole lesion being confined to an almost paper thinness of the bony cortex The periosteum is however thin and shows little or no activity the medullary canal is dilated with fibrous metaplasia of the marrow

Diagnosis—The diagnosis rests upon the x ray appearance of the shafts of the bones and the occurrence of multiple fractures It does not bear any resemblance to rickets scurvy or congenital syphilis

Prognosis—Most fetuses so afflicted die *in utero* or shortly after birth If they survive the first year of life the prognosis as to life is good but increasing disability occurs during childhood from the numerous fractures During the second decade these become less frequent and after the twentieth year they rarely occur

Treatment—Care of the child to prevent fractures in fact keeping it actually as well as metaphorically wrapped in cotton wool with a high vitamin diet to prevent any deficiency disease of childhood is the main objective Many drugs have been advocated but all are useless Archibald has attempted to prevent fractures by artificially splitting the bones longitudinally and thus producing a callous splint to the bones through their whole length It is a tedious procedure but if it can be carried out has a reasonable basis

Osteopetrosis

Synonyms—Marble bones chalky bones Albers Schonberg s disease osteo sclerosis fragilis generalisata congenital osteosclerosis and hyperostotic osteopathy

This is a comparatively rare disease of the bones which has a definite hereditary background It may be present at birth or become manifest during childhood or even later in life It is a progressive disease and affects the skull as well as the long bones The sclerosis or petrosis may first appear either at the end or in the middle of the shaft and progress centripetally or centrifugally

The patient first comes under observation either for symptoms referable to the cranium or the cranial nerves such as hydrocephalus blindness due to

Etiology—It is a congenital disease of the skeleton apparently dependent upon a nutritional abnormality during fetal life, the exact cause of which is unknown It occurs equally in both sexes

Symptoms—The signs and symptoms of this disease are confined entirely to the bones which are extremely fragile The subsequent deformities are due



Fig 438—X ray of the legs in a case of osteogenesis imperfecta showing the paper thinness of the cortex enlargement of the medullary cavity and the fracture of both femurs

to the fractures which unite normally although frequently in gross malposition (Fig 438) The callous formation is normal even at times excessive this may give to the bones an irregular beaded character best recognized by the x rays The x ray appearance of the bones is quite distinctive The remains of numerous fractures are usually obvious whether in proper alignment or leading to gross deformities, although the bones are of normal length if not shortened by frac

There has been much divergence of opinion regarding the abnormal texture of the bones which is undoubtedly due to the various stages of the disease or accidental samples of bone which have been examined There is first a period of rarefaction followed by increased calcium deposit which is of a chalky nature, but eventually the bone becomes intensely hard from osteopetrosis, and at this time it is compared with marble

There has been much discussion also of the biochemical changes in the bones, but as yet their cause is unknown It has been suggested by some that they may represent an osteoblastic stage of hyperparathyroidism, when the activity of the parathyroids causes deposition rather than metabolism of calcium but the evidence to substantiate this is quite inconclusive

As stated above the disease is progressive but it may be slowly so and individuals sometimes reach adult life without great inconvenience

Treatment so far has been of no avail

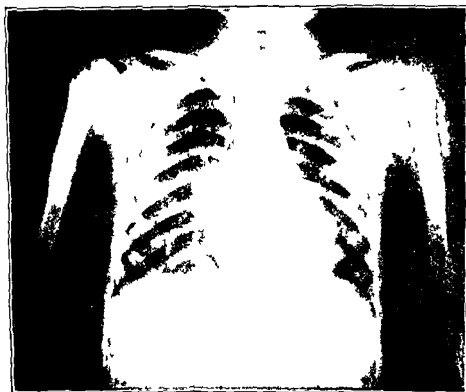


Fig 440 —X ray of the daughter of the patient shown in Fig 439 showing marble bone formation at the upper end of the humerus (Courtesy of the late Dr A Howard Pirie)

Fibrous Dysplasia

Synonym — Albright's syndrome

Definition — A rather rare congenital *fibrous replacement* of the bones and sometimes any or all of the following premature sexual development pigmentation of the skin hyperthyroidism and other more uncommon extra skeletal disturbances

optic atrophy, deafness, or some other cranial nerve palsy, or, on the other hand for pronounced anemia. The first group of symptoms are due to the encroachment of the sclerosing bone upon the various cranial foramina (Fig 422). As this is irregular in distribution the resulting symptoms may be most bizarre. The anemia results from the gradual obliteration of the medullary canal. It is usually of the myelophthisic type or of the hyperchromic type. Overactivity of the uninvolved bone marrow is indicated by an increase of reticulocytes and normoblasts in the peripheral circulation. In time a true aplastic



Fig 4 9—X ray of a e of t o t o (marbl bone or Alb rs Schonberg s di ca e) h wing th dense character of th vertebrae and the pelvic bon The patient was pregnant at the time The f tal ve tebrae re well een (Courte y of the late Dr A Howard Pirie)

anemia appears. In addition to the anemia there is also an enlargement of the liver spleen and lymphatic glands which is considered compensatory. There is also clubbing of the fingers and spontaneous fractures through areas of bony rarefaction are not uncommon. There is retarded skeletal growth which has been suggested by some as due to a pituitary origin through involvement of this gland in the bony changes at the base of the skull. There is delayed eruption of the teeth and frequently dental caries. The true nature of the disease is recognized by x ray. (See Figs 439 to 442.)

of the terminal phalanges there may also be a thickening of the bones of the forearms legs, and more rarely the femur and humerus, and slight evidence may be found in the flat bones It begins in the diaphysis as a thickening of the shaft being due to the irregular deposit of new bone under the periosteum.



Fig 441 —X ray of the leg of a case of marble bones where the lesion began in the shafts extending toward the epiphyses.

In advanced cases this appears by x ray as a shell surrounding the original shaft There is also a thickening of the neighboring soft tissues but the musculature atrophies This cannot be considered as a separate disease as it is always secondary to some visceral lesion It is rare that it assumes pronounced proportions There are remissions and exacerbations of the condition parallel with such in the original disease This is particularly notice

Etiology—This is undoubtedly a congenital disease and affects females much oftener than males

Symptoms—The symptoms are inherent in the skeletal and systemic disturbances as they appear and will therefore be considered under the following headings

Bones—The lesion in the bones is a fibrous replacement in isolated areas with apparently normal bone elsewhere One or many bones may be the site of the lesion but there is a predilection to it being unilateral These fibrous areas contain spindle cells with an indistinct cytoplasm and a pale nucleus The x ray reveals well defined areas of rarefaction Spontaneous fractures occur Calcium and phosphorus metabolism is normal

Pigmentation—This may not be present but if it is it varies considerably in area up to large patches chiefly over the sacral and lumbar regions buttocks and back of the neck The color shades from a pale fawn to a deep brown It is due to an increased number of melanoblasts and melanin in the skin and corium

Premature Sexual Development—Menstruation may start as early as two years of age and continue to be profuse but with irregular periods of duration and interval Conception has been reported as early as five years

Hyperthyroidism—This shows the usual symptoms and signs and is unusual solely on account of the early age incidence

The **diagnosis** in the complete form offers no difficulty In cases with bone lesions only, it may be confused with osteitis fibrosa cystica but the mineral metabolism clears the picture

The **prognosis** is fairly good as to life

Treatment is of no avail except in solitary cysts of the bone which may be removed and bone chips may be placed in the cavity

Other Hereditary Bone Diseases

Hereditary Arthrodysplasia and Dystrophy of the Nails—Absence of the patella and congenital dislocation of the head of the radius There may also be in association or independently absence or dystrophy of the nails

Morquio s Disease—A familial osseous dystrophy showing delay in development rarefaction and deformity of the bones of the limbs with occasionally cranial changes leading to optic atrophy

Hypertelorism—A familial tendency to excessive development of the lesser wings of the sphenoid bones leading to wide separation of the orbits and often an associated mental defect

Hypertrophic Osteoarthropathy

Synonyms—Marie s disease Hippocratic fingers

Definition—In its entirety this is a comparatively rare disease It is most frequently manifested by the clubbing of the fingers found in chronic pulmonary lesions subacute bacterial endocarditis and chronic anoxemia as in the cyanotic forms of congenital heart disease In addition to the enlargement

more frequently afflicted than females The cause has been attributed to almost every possible etiological factor that could be thought of, ranging all the way from bacterial infection, cancer trauma neurogenic factors and endocrine disorders There are only two facts of importance which might have a bearing on the etiology namely a familial history in about 30 per cent of the cases, and an unusually large incidence of arteriosclerosis or arterial atheroma Whether or not the latter is a contributing cause or an effect is unknown

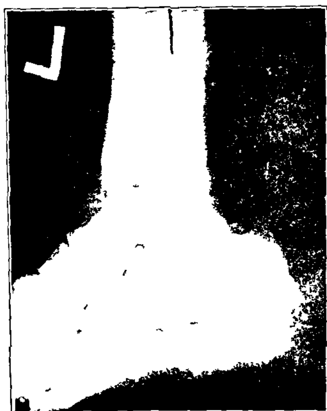


Fig 443—X ray of the lower end of the leg from an early case of hypertrophic osteoarthropathy showing the thickening under the periosteum of the anterior surface of the tibia and posterior border of the fibula

Symptomatology—The onset of the disease is so insidious that it is impossible to date its exact time and the first indication of its presence is usually found in a distortion of some single bone such as the skull or one of the extremities It may remain arrested in this stage or gradually progress to involve all the bones of the skeleton The head and mandible show progressive enlargement the spine gradually becomes bowed and rigid while the arms and legs also show bowing and great thickening The shoulder girdle and the pelvis gradually enlarge until they assume massive proportions The body is bent forward in order to maintain equilibrium and this posture with distortion of the skeleton leads to a conspicuous reduction in stature

With the gradual progression and the skeletal changes pain soon develops It varies greatly in intensity and character At times it is dull and aching

able when it is associated with bronchiectasis, pulmonary tuberculosis, or *amebic dysentery* (see Fig 443)

The diagnosis is comparatively easy, and the treatment is that of the primary disease



Fig 44 —X ray of the skull in the same case as in Fig 441 showing the increased density particularly of the base which led to optic atrophy and deafness

Osteitis Deformans

Synonym —Paget s disease

Definition —*Osteitis deformans is a chronic disease of unknown origin* affecting the bones There is extensive rarefaction and condensation which lead to enlargement and irregular deformities both of the long and flat bones

Etiology —The exact cause of this disease is unknown It usually appears between the ages of thirty and fifty seldom before or after, and males are

The x ray appearance of the skeleton is quite distinctive The calvarium becomes progressively thickened and gives the appearance as if crinkling hairs were distributed throughout The vertebrae are enlarged and appear like building blocks with absorption of their centers The long bones and ribs are *much broader than normal and show definite deformities All these bony* changes are due to the progressive condensation and absorption There is no evidence that there is a calcium or phosphorus loss but rather a redistribution

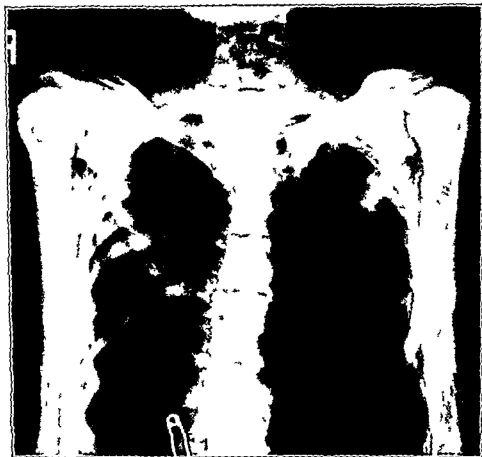


Fig 445 — X ray of the upper arms shoulder girdle and chest of the same case as in Fig 444 *showing irregular distribution of rarefaction and density particularly in the humera.* Note the dense building block appearance of the vertebrae

The analysis of whole bone shows normal proportions but if different parts of the bone are analyzed there may be found either an increase or a decrease of calcium or phosphorus depending upon the site from which the samples are taken (Figs 444 to 446)

Pathological Anatomy —The anatomical changes are chiefly to be found in the skull and long bones although the shoulder girdle pelvis and ribs are also involved in advanced cases There is evidence of progressive absorption or reduction of one part of the bone, and a condensation or ossification in other parts the latter particularly taking place in the periosteum hence the

and at others paroxysmal and violent It is exaggerated on standing or walking, and is usually worse at night The bones are tender, particularly over the anterior borders of the tibia where there may develop an associated periostitis When the disease is well established, fractures may be spontaneous or follow slight trauma Union is usually unimpaired



Fig 444—X ray of the skull in a case of osteitis deformans or Paget's disease showing the characteristic areas of *absorption* and calcification Note particularly the density of the base This case required trephining to relieve symptoms from sarcomatous degeneration causing cerebral pressure

The musculature also shares in the general condition There are cramps and the muscles gradually atrophy leading to extreme fatigue and weakness An important feature in the progressive development of the disease are cardiovascular lesions Arteriosclerosis is practically always present and of an advanced degree which in time leads to cardiac failure cerebral hemorrhage or infarctions, and symptoms of intermittent claudication Osteosarcoma is not an infrequent development as are also degenerative and chronic infectious diseases of the lungs, such as chronic bronchitis tuberculosis, and emphysema

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Paget s disease it is only a superficial resemblance and a positive Wassermann usually indicates in the former the proper diagnosis Osteomalacia occurs usually in young women and there is deformity with little increase in size atrophy being more prominent than hypertrophy Osteitis fibrosa cystica may give a clinical appearance of bony enlargement but this is due to fibrous metaplasia Cysts are more prominent and fractures more frequent while the skull usually escapes The x ray differences are quite distinctive

Prognosis —The patient seldom dies of osteitis deformans unless from progressive cachexia Cardiac and vascular lesions malignant disease and pulmonary tuberculosis are the most common causes of death The disease however is essentially a chronic one and finally may render the victim a complete cripple It is not unusual for the disease to become quiescent or arrested and all symptoms disappear leaving the established deformities Cases have been reported where improvement has occurred

Treatment —There is nothing that can be done in a specific way to arrest the disease There have been reported isolated cases that seem to respond favorably to a variety of so called cures but there is nothing to suggest that these were not mere coincidents Orthopedic procedures may be necessary to improve function but these are symptomatic measures

General Hyperkeratosis of the Skull

Synonyms —Megalocephaly leontiasis ossia

Definition —This is a rare disease characterized by great increase or hyperostosis of all the bones of the skull including the mandible This growth may be either eccentric or concentric The overgrowth encroaches upon the cerebral cavity and the bony canals being particularly prominent in the orbits and accessory sinuses The texture of the bone is extremely hard resembling ivory It is rare that other bones of the skeleton are involved Irregular growth or exostoses do not occur

Symptoms —The symptoms are bizarre as they are made up of the results of cerebral nervous and vascular pressure The principal ones are headache and exophthalmos but there may be also cranial nerve palsies insomnia mental disturbances even to insanity and convulsions Pressure on the veins produces a greater effect than that on the arteries therefore there may be superficial varicosities and signs of intracranial vascular engorgement due to venous stasis The *cause* is quite unknown although it is more frequent in females than in males

Diagnosis —The diagnosis is usually quite easy except in the earliest stages It must be differentiated chiefly from acromegaly and Paget s disease The *course* is insidious and prolonged usually lasting from thirty to forty years Occasionally it may become quiescent There is no *treatment* known and when intracranial pressure is sufficiently severe decompression is necessary

Acrocephaly

Synonyms —Oxycephaly tower head steeple head

Definition —This is an unusual disease in which there is a progressive upward enlargement of the cranium as if it were being pulled up to a point

progressive enlargement of the bony diameters This is irregularly distributed and therefore on section shows a varied appearance Cysts are rare and do not assume large dimensions

Diagnosis —There is little difficulty in differentiating this disease from other bony lesions It may be confused with acromegaly, osteoporosis senilis, osteomalacia, syphilitic periostitis or sabre shin, osteitis fibrosa cystica, and



Fig 446 —X ray of the lower ends of the femora and upper ends of the tibia of the same case in Fig 444 and 445

the adult manifestations of severe infantile rickets There are, however particular points about all of these that can easily differentiate them from osteitis deformans In acromegaly the calvarium and long bones are not affected, osteoporosis is seen in the later decades and is an atrophy rather than a deformity The sabre shin of syphilis and the boomerang shin of Australia and New Guinea are found only in the tibia and although here it may simulate

Paget s disease, it is only a superficial resemblance and a positive Wassermann usually indicates in the former the proper diagnosis. Osteomalacia occurs usually in young women and there is deformity with little increase in size, atrophy being more prominent than hypertrophy. Osteitis fibrosa cystica may give a clinical appearance of bony enlargement but this is due to fibrous metaplasia. Cysts are more prominent and fractures more frequent while the skull usually escapes. The x ray differences are quite distinctive.

Prognosis—The patient seldom dies of osteitis deformans unless from progressive cachexia. Cardiac and vascular lesions, malignant disease and pulmonary tuberculosis are the most common causes of death. The disease, however, is essentially a chronic one and finally may render the victim a complete cripple. *It is not unusual for the disease to become quiescent or arrested and all symptoms disappear leaving the established deformities.* Cases have been reported where improvement has occurred.

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like a bell tent, and in so doing the supraorbital and temporal ridges and the malar and maxillary prominences are flattened, with decreased volume of all the paranasal sinuses (Fig 447) The whole expression is one of vacancy except for the exophthalmos which is constant and gives to the face a most startlingly absurd appearance This is due to the progressive shallowness of the orbital cavities It may be impossible to close the eyes and in consequence keratitis and conjunctivitis occur There is also optic atrophy with engorgement of the veins, and errors of refraction are constant Headaches, vomiting, and other signs of intracranial pressure are common Convulsions have been reported in children This abnormality does not seem to influence the length of life Blindness and deafness are frequent sequelae

Treatment —There is no treatment known which has any effect on its progress, although cranial decompression may sometimes be necessary



Fig 44 —X ray of the skull in a case of acrocephaly Note the obliteration of the sutures conspicuous convolutional markings short and deep frontal and temporal fossae and the enlargement of the sella from pressure Trephining was necessary to relieve symptoms (From the Montreal Neurological Institute)

DISEASES OF THE MUSCLES

Introduction

One of the most common complaints met with in general practice is pain in the limbs, variously attributed by the patient to the muscles bones, ligaments, and nerves It may follow exposure to cold unusual exercise trauma or be associated with changes in barometric pressure and often forms a group of prodromata to infections which may eventually culminate in a severe spe

cific disease or a fleeting upper respiratory infection The classification of these vague pains and aches is almost an impossible task There is no doubt that some of them can be definitely attributed to either local or general intoxication, but that they are due to a localized action of bacteria seems problematical Those due to trauma are quite easily explained, and it is probable that those following unusual exertion are due to muscle fatigue and local capillary circulatory disturbances with possible local accumulations of lactic acid or other products of muscle metabolism It is well known that they are best treated by a continuation of muscular activity Another common cause which is too frequently overlooked is muscular tension the result of maintaining an unusual position A good example of this is pain in the muscles at the back of the neck spreading over the shoulders due to holding the head in a tense position through maladjustment of bifocal or other types of complicated eye glasses There seems little doubt that many cases of lumbar pain are due to bad static posture as are pains in the lower legs the result of flat feet The search for the cause of these discomforts is divisible into two lines of investigation If the pain remains local and constant in distribution it is reasonable to surmise that the cause is local If on the other hand the pain be more diffuse and intermittent it is to be expected that the cause will be of a systemic character It is unwise to give a dogmatic diagnosis until a careful search of the cause has been carried out and all possible factors have been analyzed Although the pain or ache may seem insignificant in itself it is often the first manifestation of a serious local or systemic disease as for instance pain low in the back may be due to carcinoma of the prostate or rectum while vague fleeting pains in the thighs may indicate pressure on the lumbar nerve roots On the other hand a searching general examination including many laboratory procedures would not seem justified in every vague ache or pain It is in such cases that the acumen of the clinician is of the greatest value to the patient

When the pain is localized a careful examination may reveal points of tenderness either in the subcutaneous or deeper tissues a sense of resistance or rigidity in the muscles or perhaps the patient complains of a definite radiation These findings immediately suggest a local subcutaneous lesion or a muscle spasm which may be due to a variety of causes or third some condition which is producing local nerve or root irritation and hence the radiation over its distribution If on the other hand the discomfort is more diffuse and changes from hour to hour and day to day the cause is usually to be found in some far distant area and if unusual exercise and signs of a general infection suggesting the onset of some systemic disease can be eliminated a thorough search must then be made for some focal source of infection or intoxication Much harm has resulted from dismissing such symptoms too lightly The patient receiving little sympathy or attention is likely to seek relief from one of the irregular cults or after silently suffering for a space of time returns in desperation for relief and the cause is now obvious but much time has been lost when treatment can do the most good

Out of this indefinite group of symptoms there crystallizes a number of conditions which may be labeled by many synonyms such as myalgia, fibrositis,

panniculitis, lumbago, muscular rheumatism, etc Some of these when applied in a strict sense have a reason for their existence, but unfortunately they are used so loosely that they may mean something or nothing If they are applied in their strict pathological sense, a *fibrositis* would mean a local or general inflammation of the fasciae, muscle sheaths, ligaments, aponeuroses and tendons Such cases are not unusual Their general symptomatology is pain, "stiffness of the joints" and muscular weakness On examination localized tender areas may be found which also give the impression to the palpating finger of local areas of induration

Myositis strictly means an inflammation of the muscles, and *panniculitis* an inflammation of the subcutaneous fatty tissues Where fibrositis, panniculitis, and myositis begin and end or when they are all part of a local lesion is difficult to determine Painful nodules may be palpated in all of them They are all aggravated by muscular movement If not due to a local cause such as trauma, they all have a tendency for remissions and exacerbations unless the original cause is removed Local disturbances of this nature have given rise to a nomenclature which has implied definite diseases and is used as such not only by the laity but also by the profession In this category may be placed neuralgias pleurodynia, torticollis, lumbago indurative or nodular headache sciatica etc It cannot be denied that some of these by their local persistence may in time lead to local anatomical changes and may be most intractable to therapeutic measures, but this does not remove the possibility that in their earliest stages they could have been cured if they had been taken with sufficient seriousness and the local or general cause sought and removed

There are in addition to these vague signs and symptoms, certain well defined lesions of the muscles and associated tissues of which the following are the most important

Primary Suppurative Myositis

Definition—This is an acute inflammation of the muscle which may be either single or multiple, and has associated signs of acute infection

Incidence—It is a comparatively rare disease in North America, and has been most commonly described in Japan and tropical Africa where it goes by the name of "myositis purulentia tropica"

Etiology—It is found in both sexes and at all ages and is usually attributed to an infection by the *Staphylococcus aureus* the portal of entry of which is not constant

Symptoms—The onset is sudden with a chill and pyrexia This is also accompanied by the usual general symptoms of infections such as malaise anorexia headache generalized pains and sweating In a short time localized areas of swelling, tenderness and induration are found in the muscles involved These may be isolated or occur in groups which may eventually coalesce to form large abscess cavities Over them there may be redness and ecchymoses dependent upon how close they approach the surface of the skin. In a week to ten days fluctuation is apparent

Pathological Anatomy—The anatomical changes are those of suppurating processes within the muscles with extensive surrounding round cell infiltration Not only is the muscle itself involved but also its sheath The tendons and subcutaneous tissues and skin may *also be affected In other words it is a* deep seated disease which may penetrate to the surface or along the muscle planes It gives all indications of being a pyemia with a special selectivity for the muscular tissue

Diagnosis—At the onset this disease is usually confused with any one of the acute infectious diseases *that has an abrupt onset but as soon as the signs* of local muscle induration are developed, the real diagnosis is apparent It is further confirmed by local areas of fluctuation

Prognosis—The muscular abscesses seldom resolve spontaneously and if properly treated healing soon occurs but there is usually a residue of mus *cular atrophy*

Treatment—In the early stages local heat or cold to relieve pain is indi cated as well as the general treatment of any acute infection As soon as fluctuation is detected free surgical drainage should be carried out If con tractures either from malposition or scar tissue eventually develop these should be treated by local *passive and active movement and massage* and if neces sary orthopedic measures

Dermatomyositis

Synonym—Nonsuppurative myositis

Definition—This was *at one time principally known by its synonym It* is characterized by a triad of edema dermatitis and myasthenia

Incidence—It was formerly considered a rare disease in North America and reported chiefly from the Scandinavian countries In recent years more cases are being recognized here This is probably due to the fact that the com plete clinical pattern is now appreciated as distinct from its several parts

Etiology—The cause is unknown It is now classed among the group of so called collagen diseases concerning which there is much debate as to etiological factors Among these a direct or systemic effect of bacterial tox ins upon collagen tissues has been advanced while others have suggested an allergic basis It is most common in middle age next in children but all decades may be affected and equally in both sexes

Symptoms—The onset is occasionally preceded by a history suggestive of transient Raynaud s disease otherwise it is insidious with prodromata of weakness malaise and anorexia This is soon followed by a rapid appearance of more or less diffuse pains and aches which are soon localized in the muscles *rather than the joints and periarticular tissues One group of muscles after* another may be involved until practically the whole musculature has been the site of the lesion The pain is excruciating and is variously described as boring tearing or cramplike ' There is exquisite tenderness

The skin lesions are fairly characteristic In about one third of the cases there is erythema and edema of eyelids and face which is diffuse and of a heliotrope color similar to that found in **Lupus erythematosis disseminata**

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groups of muscles involved, while in other cases it may progress to affect all voluntary muscles There is no sensory change while the electrical reactions in some cases may be reduced and in others lost

Pathological Anatomy—The anatomical changes are first local swellings which are extremely hard The muscle fibers are eventually replaced by connective tissue the former undergoing hyaline degeneration There may be local areas of edema of the skin and connective tissue The muscles cut with great difficulty, being almost as hard as wood

Diagnosis and Treatment—An exact *diagnosis* rests upon biopsy examination As already mentioned there may be extensive progression although in time some improvement usually occurs The *treatment* is purely symptomatic

Myositis Ossificans Progressiva

This is a terminal inflammatory lesion of the muscles which eventually become ossified There is no cause known

Symptoms—The onset of the disease is insidious with vague localized or radiating pains in the limbs It has been described by Munchmeyer as divisible into three stages In the first stage there is extensive infiltration both within and between the muscle which leads to the formation and proliferation of connective tissue It appears to have its origin about the blood vessels In the second stage the connective tissue becomes much more dense and begins to contract to form hard fibrous masses which include muscle fibers In the center of these fibrotic areas osteotrabeculae begin to appear which later form osteoblasts and the third stage develops with the ossification of compact and spongy bone This new bone develops also in the fasciae ligaments and tendons and resembles normal bone At times there is edema of the subcutaneous tissues and redness of the skin and pyrexia but this lasts only for a few days When at rest pain is not a prominent symptom although at night there may be shooting pains in the limbs The rest of the symptoms and signs are due to the contractures and fixation of the joints by the ossified soft parts The muscles of the back and neck are first involved and it then spreads to the upper and lower extremities and the face The hands and feet are the last affected Exostoses are not uncommon The changes in the muscles are readily detected by the x ray once calcification has begun In about 75 per cent of the cases there is a peculiar anomalous deformity of the great toes and thumbs which is due to the retardation of growth of the metatarsal and metacarpal bones with ankylosis

Diagnosis—The diagnosis in the early stages may be difficult but it is usually certain once the deformity of the thumbs and great toes exostoses and bony deposits in the muscles appear, which can be recognized by the x ray

Prognosis—The prognosis as to life depends upon the degree of the deformity and the rapidity with which complete incapacity develops There may be difficulty in mastication and respiration due to ossification of the muscles required for these acts Treatment is of no avail to control the ossification but careful nursing is important to prevent complications and maintain nutrition

(see page 1411) It has also been described as erysipeloid, roseolar, morbilliform, urticarial, eczematous, and petechial Almost any combination within these descriptive terms may be found and may affect any part of the skin

The edema may be localized in the skin lesions or it may be diffuse and simulate scleroderma In many areas it seems to penetrate deeply through the subcutaneous tissues to the muscles themselves The edema would appear to be a common attribute of both the skin and muscle lesions

In addition to the skeletal muscles those of the tongue pharynx larynx esophagus diaphragm and intercostals may be involved

Fever is irregularly present and the spleen is often palpable There is a leucocytosis and in about one fifth of the cases an eosinophilia is present An excessive creatinuria is the rule Nephritis is not uncommon

Pathology—Biopsies of the skin when taken early are almost undistinguishable from scleroderma The skin shows considerable edema and engorgement the subcutaneous tissues are also edematous with a yellowish serous fluid The muscles are swollen pale and also edematous and undergo degeneration The smaller blood vessels are the site of definite "fibrinoid" degeneration with straightening and thickening of the collagen fibers and evidence of friability and smudgy eosinophilic staining There is also thickening of the smooth muscle of the media infiltration of the connective tissue fibers thickening of the intima and finally obliteration with thrombus formation Cellular infiltration is not conspicuous and occurs in the perivascular connective tissue and in the muscle planes

Diagnosis—The diagnosis is not easy in the early stages but if it be considered many more cases will be recognized and may perhaps be confirmed by biopsy It is usually confused with erythema nodosum lupus erythematosus disseminata scleroderma rheumatoid arthritis and persistent rheumatic fever

Prognosis—This is serious as over 50 per cent of the patients in the cases collected by Steiner died usually due to involvement of the myocardium or the muscles of respiration or deglutition In those that survived the edema and skin lesions disappear with atrophy of the skin which becomes boardlike with a brawny texture identical to scleroderma The muscles atrophy and shrink leading to contractures

Treatment—The treatment is purely symptomatic rest in bed and analgesics to relieve the intense muscular pain

Myositis Fibrosa

(Myositis Chronica)

Myositis fibrosa is an unusual affection of the muscles, of unknown origin It is characterized by an insidious onset, and successive groups of muscles are gradually involved It usually first appears in the legs The most prominent symptom is pain, particularly on movement which eventually forces the patient to bed The muscles become rigid and contractures usually in the flexor position, eventually develop It may become arrested with one or more

TABLE XV

SITUATION	BURSA INVOLVED	SYNONYM
Shoulder	Acromion	*Hod Carrier's Bursitis*
Elbow	Radio Humeral	—
	Olecranon	Miner's Elbow
Hip	Trochanteric	—
Knee (superficial)	Prepatellar	Housemaid's Knee Nun's Bursitis
	Tibial Tubercle	—
(deep)	Infra patellar	—
	Gastrocnemius	—
	Medial Tibial (Anserine)	
	Posterior Tibial (Biceps)	—
Foot	Posterior Calcaneal	—
	Anterior Calcaneal	—
	Anterior Plantar	—
	Lumbrical	—

more acute forms this may be considerable while in the chronic types there is usually less secretion and the thickened surfaces may be in apposition

Treatment —The treatment in the acute phase is complete rest with fixation of the part and the application of lead and opium fomentations If the process progresses into a chronic form it may be necessary either to remove the bursa or to destroy it by curettage a gauze pack kept in position to allow the wound to heal completely

DISEASES OF THE JOINTS

Introduction

There is probably no group of diseases in which there is so much confusion as those where the symptoms are localized about the joints unless it be diseases of the kidney This is probably due to the fact that many structures are involved in the constant joint movements of daily activity Therefore any pain stiffness or discomfort which may be felt is automatically referred to the joints although the articular surfaces may in no way be involved Furthermore pains in the limbs are of common occurrence not only during the onset of acute infections but also with changes of barometer, after unaccustomed exercise trichiniasis and a host of other diverse conditions In addition there may be definitely local disturbances which have already been mentioned such as *fibrositis panniculitis fasciculitis neuritis* neuralgias myalgias, bursitis etc It is seldom that the lesions in arthritis do not involve the periarticular tissues also which may lead to confusion as to what degree of the signs and symptoms are intraarticular and how much is periarticular

The multiplicity of factors which may cause arthritis makes a simple classification difficult Some of these have been dealt with in detail elsewhere and therefore will only be mentioned to recall the fact that they form part of this large group The principal metabolic disturbance is gout which has already been considered (see page 870) Neurotrophic conditions are represented by the Charcot's joints of locomotor ataxia and syringomyelia and to a less definite degree by intermittent hydrarthrosis In all hemorrhagic con

Localized or traumatic ossifying myositis may follow a severe muscle injury. It remains localized and if the underlying bone has also been injured, the bone, muscle, and fibrous tissue may be consolidated into one bony mass.

Myalgia

In the introduction to this section reference was made to the vague and sometimes acute local muscular pains with muscle spasm. This is a comparatively common condition and chiefly is found in the muscles of the lumbar region (lumbago), in the trapezius (trapezius myositis), and in the cleidosternomastoid (torticollis). Many agents have been ascribed as causing these conditions. They are sometimes most intractible to treatment, but principally they are of importance in the differential diagnosis of other conditions which may give pain in these particular regions, especially is this so in the first two. It is difficult to classify them as separate diseases, although localized induration may sometimes be detected on palpation. If after a most thorough search no general or local cause can be found for the pain and rigidity of the muscles the condition is best treated by analgesics and salicylates, and local applications of heat, massage, and acupuncture.

Bursitis

There are placed in different parts of the body, structures called bursae which are serous lined compartments situated where there is friction by the movement of soft parts over firmer and more deeply placed structures. The topography of many of these is well known, but connective tissue has the capacity of producing new bursae if they are required on account of oft repeated but unusual types of movement in the limbs. Therefore they may be found in situations which are not considered to possess them.

Symptoms and Signs.—The symptoms and signs of bursitis are usually constant and are only modified by their situation. The principal one is *pain* on movement of the part, due to the rubbing together of the inflamed and roughened serous surfaces. There is also local tenderness and frequently swelling due to a serous exudate into the sacs which at times may be acutely inflammatory with round cell and leucocytic infiltration and exudate. The pain is relieved when the surfaces are separated by exudate unless there is surrounding inflammation.

The bursae are most numerous about the knee where Virchow found seventy, although they were not all constantly present. It would not serve a useful purpose to describe the clinical features of all in detail. The bursae principally affected are given in Table XV.

Pathological Anatomy.—The anatomical changes in bursitis are common to all sites. The endothelial cells may fail to secrete the viscus serous fluid which prevents friction and for which purpose the bursae are formed. The lining may be thickened and changed from a single layer of flat cells to several layers, and they may become *cuboidal or columnar in shape*. The degree of acute inflammatory reaction varies considerably from case to case. In the

meningococcus, tuberculosis brucellosis dysentery influenza *Oidium coccidioides* glanders smallpox measles and diphtheria

Symptoms—The symptoms vary with the severity of the local lesion Pain is present but varies considerably not only in different joints of the same case but in different cases The vague pains of spondylitis and hip joint disease are often mistaken for neuritis, sciatica, myositis, fibrositis, etc The pain due to arthritis is aggravated by movement and has associated with it muscular spasm atrophy and frequently deformity In the more superficial joints such as the shoulder elbow wrist knee and ankle and the smaller joints of the hands and feet, local swelling, tenderness, redness and limitation of movement are conspicuous signs If the arthritis develops during the course or convalescence of one of the diseases mentioned above there is little doubt as to the etiology In addition to the local signs there may be pyrexia chills and sweats, particularly if there is a purulent process within the joint

Pathological Anatomy—The anatomical changes vary considerably from a mild inflammatory reaction to considerable destruction not only of the synovial membrane and cartilages but also of the periarticular tissues and perforation of the joint with sinus formation may occur The inflammatory reaction is similar to that which would occur with the specific organism in other tissues

Diagnosis—The diagnosis depends upon the appreciation of the possibility of a secondary or metastatic arthritis occurring in the course of a specific acute infection The mistakes of omission are most frequent when the spine or hip joints are involved and as has been intimated above the arthritis may be mistaken for milder and less serious causes of local pain The true diagnosis is usually arrived at by a careful history, the local symptomatology and x ray examination The more indolent forms such as those due to tuberculosis syphilis and typhoid fever often give more difficulty

Prognosis—The prognosis depends upon the infecting organism The most serious are lesions due to meningococcus staphylococcus, streptococcus and the oidium coccidioides

Treatment—The treatment is in the first instance that of the general disease which has caused the arthritis The local treatment consists of rest heat or cold and such specific therapy as may be indicated It is well to immobilize the joint or joints either in splints or in plaster of Paris shells to prevent contractures and other disabling postural effects If a purulent exudate is excessive aspiration of the joint cavity is indicated, and when there is evidence of local destruction surgical interference with free drainage may be imperative Each case and joint must be dealt with on its own merits

Chronic Nonsuppurative Arthritis

We have now to consider a group of cases of arthritis which are in a state of considerable confusion There are numerous classifications and synonyms are used by different authors to mean different things Some of these are the following rheumatoid arthritis arthritis deformans osteo arthritis hypertrophic arthritis degenerative arthritis senile rheumatism chronic rheumatism atrophic arthritis infectious arthritis, etc The confu

ditions extravasations into the joints may occur, and these are principally represented by hemophilia and scurvy In fact, in the former disease limitation of movement of one or more joints subsequent to slight trauma may be an outstanding feature Trauma may also produce a local arthritis and where there is dislocation of the semilunar cartilages of the knee joint recurrent pain and effusion into the joint may lead to considerable impairment of function There are also cases which can be attributed to occupational or postural strain Primary or metastatic tumors may invade the joint, producing local arthritic lesions Disturbed joint function can also be attributed to contractures resulting from local nerve injuries, or the results of poliomyelitis or hemiplegia Arthritis is often associated with serum sickness, and occurs in those sensitive to foods or other allergens In all of these conditions there is either a *local or systemic* cause which can be detected as a rule There are, in addition, certain local disturbances of the bone in apposition to a joint which may lead to disability Among these may be mentioned osteochondritis, Perthes' disease, and Koehler's disease, descriptions of which will be found in textbooks on orthopedics or surgery

There now remain to be considered three groups of arthritis, *namely*, the septic arthritis, chronic nonsuppurative arthritis, and osteoarthritis

Septic Arthritis

Septic arthritis is frequently called infective arthritis which however, is a designation which leads to confusion In all these cases a microorganism is present in the joint cavity It may be carried there by the blood stream, or a septic focus in the neighboring bone may rupture into the joint, or it may be induced through a penetrating wound The second and third causes do not particularly interest us at the moment as they are purely local lesions and are obvious both as to etiology and treatment

Septic arthritis due to the transportation of microorganisms by the blood stream is always secondary or metastatic to some systemic infection It is principally caused by the streptococcus as in cases of streptococcal septicemia, *erysipelas* and *scarlet fever* *In the last disease there* may be an arthritis which is difficult to distinguish from rheumatic fever This has already been dealt with In other cases there is a frank suppurative process occurring in one or more joints In these cases cardiac involvement does not occur The other organisms which play a part in producing septic arthritis include the *staphylococcus gonococcus pneumococcus treponema* pallidum and typhoid bacillus The arthritis due to such organisms is usually an exudative process but during convalescence from typhoid fever the so called typhoid spine or hip may develop There has been considerable discussion as to whether typhoid spine is a neurosis or is caused by definite anatomical changes The same may be said *of the similar affection of the* hip In some instances a chronic osteitis of the hip and neck of the femur has been found and also occasionally x ray evidence of a spondylitis has been detected The majority of the cases, however do not show organic changes Specific infectious diseases which may less frequently cause arthritis as a secondary lesion are

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sion will be more confounded if a rigid classification is constructed upon definite anatomical changes, as these are not always constant throughout the whole course of the disease When the different synonyms are sorted out there will be found two main varieties of arthritis, as follows rheumatoid arthritis, arthritis deformans, atrophic arthritis, proliferative arthritis, all being applied to more or less the same symptom complex, and the second group will comprise osteoarthritis, hypertrophic arthritis, degenerative arthritis, and such local arthritic diseases as morbus coxae senilis, and Heberden's nodes In the present description the terms "rheumatoid arthritis" will be used to signify the first group and "osteoarthritis" the second

Rheumatoid Arthritis

Etiology—The etiology of this disease—if it be a specific disease—is not known The causes which have been considered as playing a part in its production may be divided into the predisposing and the exciting Among the former have been included physical and emotional shock, trauma, exposure to cold and dampness fatigue, constitutional characters, heredity, climate etc Most of these have been accused of being predisposing factors in many chronic diseases It is common in the history of a case of rheumatoid arthritis to find a record of other members of the present or past generations having suffered from a similar disease It is a disease of the temperate zones being rarely found in the Tropics The first manifestations usually appear before the thirty fifth year It is not unusual to encounter severe cases with considerable deformity and rapid muscular wasting in young unmarried women These have been considered by some to be connected with the sexual cycle The author has known married women who were only free of symptoms when pregnant but after the thirteenth and fourteenth child this prophylaxis seemed to have been carried to a reasonable limit Jaundice has been reported as having a similar effect

The exciting causes of this disease continue to be a matter of controversy which revolves around the decision as to whether it be an infectious disease or not The principal evidence marshalled in favor of its being so is the supposed frequency of focal infections about the teeth in the tonsils paranasal sinuses, gallbladder prostate colon, cervix uteri, and pelvic adnexa It is quite true that such an infection may be found in a person with rheumatoid arthritis but on the contrary, they are also found in as many, if not more that do not have this disease It is still far from proved that focal infections are directly responsible for this disease Another school of thought has been in favor of the disease being an allergic phenomenon Considerable fragmentary evidence can be marshalled in favor of both theories Particularly in favor of the first has been the finding by Cecil Nicholls and Stainsby, of an attenuated streptococcus in the focal infections a similar streptococcus being recoverable from the blood and joints in a goodly percentage of patients a higher agglutinin titer for the *Streptococcus hemolyticus* in their blood as compared to controls high precipitation of the streptococcus protein and carbohydrate with the serum of these patients and finally the production of a chronic progressive

arthritis by repeated streptococcus injections in rabbits which closely resembles rheumatoid arthritis in man The first and last of these points have not been by any means unanimously accepted, and the second and third have been claimed to indicate an allergic condition Other conditions which have been suggested

Fig 448 —Photograph of the hand in a case of rheumatoid arthritis in the acute stage showing swelling of the wrists and fusiform enlargement of the fing

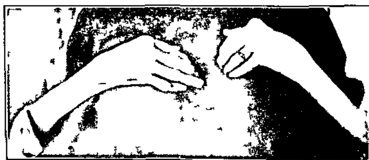


Fig 449 —Photograph of the hand in a case of arthritis deformans showing atrophy fusiform swelling of the fingers and ulnar deformity

as being exciting factors in this disease are various anatomical changes in the gastrointestinal tract particularly a redundant and hypotonic colon and finally more recently Rinehart has shown experimentally an important rela

tionship between the joint lesions of scurvy, rheumatic fever* and rheumatoid arthritis, and those produced in animals by a deficiency of vitamin C It would be unwise to be dogmatic as to the cause of this disease at the present juncture There is something to be said in favor of any of these causes being operative, but none of them are beyond reproach, and all are open to considerable criticism

Recently it has been suggested that rheumatoid arthritis should be grouped with the so called "collagen diseases" This has been based on the widespread finding of fibrinoid degeneration of the collagen or fibrous connective tissues This does not carry the question of etiology to a more definite conclusion but it does emphasize the concept that this is a systemic disease and that the arthritic manifestations are only one evidence of a widespread process

Symptoms—The onset of rheumatoid arthritis may be either acute or insidious In about 50 per cent of the cases it can be definitely dated, and is often accompanied by low grade pyrexia, headache, general malaise, and frequently splenomegaly and lymph adenopathy The joint symptoms in the beginning may be migratory The first to be involved are usually the knees and fingers, followed by the shoulders wrists, ankles, elbows, until ultimately practically every joint in the body can be affected

When the onset is insidious one joint only may be affected, and remain so with varying intensity for weeks or months Gradually other joints follow until eventually both the acute and the insidious reach the same stage

The local disturbances are a variable degree of pain which is not always in proportion to the swelling This latter is best seen in the fingers which have a fusiform or sausage like shape In time contractures lead to considerable deformity in these parts There is often flexion of the proximal phalanges and hyperextension of the terminal ones, while other joints show lateral deflection and subluxation which combine to produce quite bizarre deformities (see Fig 449) The larger joints are similarly affected and exhibit swelling local redness increased local temperature tenderness, and effusion

The constitutional symptoms are important Secondary anemia and considerable emaciation are the rule in well established cases Good nutrition and no anemia is the exception Apart from the local heat about the joints, the limbs are usually cold and clammy and there is lowering of the surface temperature probably due to vasoconstriction of the capillaries which are conspicuously restricted both in numbers and size There is also a lowered sugar tolerance and the sedimentation rate is rapid All these systemic reactions point to a general disturbance of the physiological control

It must be appreciated that all cases of this disease do not present the classical features as here described There are many variants in the extent and severity of the arthritic changes and systemic reactions It may be taken as a general rule that the younger the victim the more violent is the disease It is the irregular case that gives the most trouble in assessing the true nature of the disease

* It might be considered advisable to deal with rheumatic fever amongst diseases of the joints but, the author does not consider this proper as the arthritis in this disease is merely an incident In spite of the fact that fibroid nodules develop in both diseases and occasionally cardiac lesions occur in cases which are supposed to be arthritis deformans

There are several forms of this disease which warrant special mention The first is a spondylitis which is described as the ' Marie Strumpell'' type It is characterized by the so called poker spine' caused by the vertebrae being bound together into a solid mass by fibrous tissue (see Fig 450) It is interesting to note that the lesion begins in the vertebral joints where a pannus



Fig 450—X ray of the spine showing the spondylitis of the Marie Strumpell type

destroys the intravertebral discs in a manner similar to that in classical arthritis deformans But in distinction to this form the smaller joints of the hands feet fingers and toes are seldom involved nor is there the wasting of the muscles of the hands feet legs and forearms The vascular and thermal changes of the skin etc also are not found On the contrary the larger joints particularly the hips and shoulders are likely to be affected either in sequence or independ

ently It is most important to appreciate that in classical rheumatoid arthritis the progress of the joint involvement is usually centripetal, while in the "Marie Strumpell" form it is centrifugal

The second type requiring special mention is an acute to chronic arthritis in children, "Juvenile arthritis deformans," or "Still's disease" (see Fig 451) In addition to the joint lesions which are similar to those of rheumatoid arthritis there is a lymphadenopathy, splenomegaly and hepatomegaly and amyloid degeneration of the viscera has been reported Felty, in 1924, described a group



Fig 451 —Photograph of a child with juvenile arthritis deformans or Still's disease

of cases in adults which were characterized by arthritis, splenomegaly and leukopenia He considered it a specific syndrome and it became known by his name It is now not considered to be a separate disease but an atypical form of rheumatoid arthritis related except for the age period to "Still's disease"

The x ray findings in rheumatoid arthritis and "Still's disease" chiefly consist in a narrowing of the articular spaces a rarefaction of the bones and finally a complete destruction and fusion of the articulating surfaces showing no lipping or spurring but the fusion may be a bony ankylosis with extension of the bone marrow from one bone to another The loss of contour and the

fusion of the bones is best seen in the wrists and fingers The contractures produce subluxations which can be detected by palpation and by the x ray which often reveal the articulating surface of one bone impinging upon the shaft of its neighbor

Small punched out areas are often seen in the smaller bones This may closely resemble the x ray lesion seen in gout and Boeck s sarcoid Indeed, the differential x ray diagnosis may be extremely difficult

Pathological Anatomy —The first and most characteristic anatomical finding is the development of a pannus within the joint due to proliferation of a synovial membrane This is eventually converted into granulation tissue which spreads over the whole cartilage producing extensive destruction of it

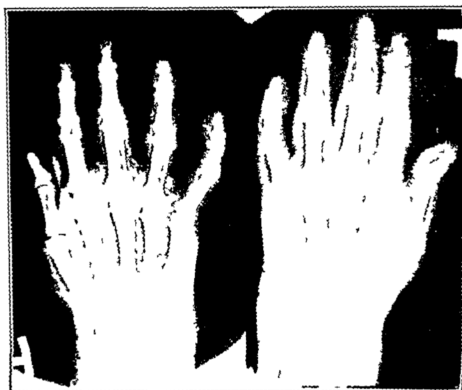


Fig 45 —X ray of the hand in a case of arthritis deformans showing decalcification narrowed joint spaces and soft tissue swelling

This proliferative process finally involves the capsule and periarticular structures It is a true inflammatory process and in time leads to complete destruction and obliteration of the articular cavities Fibroid nodules similar to those encountered in acute rheumatic fever are sometimes found

There was referred to above under Etiology the systemic finding of a diffuse fibrinoid degeneration of the collagen tissues This is widely distributed through many structures wherever these tissues may be found It therefore raises the concept of rheumatoid arthritis including most of its variants from that of a local lesion to the status of a systemic disease in which the

joint lesions are but a visible manifestation Without this appreciation of the general character of the disease, the approach to its proper handling is unrealistic

Diagnosis —In a well established case the diagnosis is seldom in doubt The more important points to differentiate it from other joint lesions are its occurrence in young adults, the migratory character of the arthritis, the characteristic form of the fingers and the presence of a general systemic reaction indicated particularly by pyrexia, emaciation, muscular atrophy, lowered surface temperature of the extremities, and local sweating The arthritis itself may be confused with subacute and chronic septic arthritis, particularly the gonorrheal form, subacute and chronic rheumatic fever, gout, and osteoarthritis



Fig 453 —X ray of the hands in a case of rheumatoid arthritis in a more advanced stage than seen in Fig 45 showing destruction of the carpal bones and decalcification

Its differentiation from gonorrheal arthritis is based upon the presence of a specific pelvic or prostatic infection, although this is not absolutely necessary as the signs of infection at the portal of entry may have disappeared and still an active arthritis may be present It can be further differentiated by the fact that gonorrheal arthritis usually localizes in one or more of the larger joints The diagnosis may be aided by the presence of a positive gonorrheal fixation test Subacute and chronic rheumatic fever can give rise to considerable difficulty in diagnosis It must be remembered that this infection varies in the intensity of its local manifestations at different age periods In childhood the cardiac and nervous symptoms dominate the picture, but if

the first attack occurs after thirty these symptoms may be comparatively insignificant and the main features are arthritic signs a low grade persisting pyrexia, a slight leucocytosis and sweats There is also an increased sedimentation rate and in these cases fibroid nodules of a gross character are not unusual Of considerable importance in these cases is the detection of a prolongation of the P R interval in the electrocardiogram *It may take some*



Fig 454 —Fibroid nodules about the elbow in a case of rheumatoid arthritis Note also the deformity of the fingers



Fig 455 —Photomicrograph of a fibroid nodule shown in Fig 454

time before a differentiation of diagnosis can be arrived at The prognosis in the two conditions is quite different, being more favorable in the chronic rheumatic fever at this age

The incidence of gout in North America has not received the attention which it should in recent generations It is more likely that a case of gout would be confused with rheumatoid arthritis than the contrary The characteristic x ray findings and the high uric acid in the blood should readily clarify the diagnosis if gout is considered as a possibility The differential diagnosis of rheumatoid arthritis and osteoarthritis often presents considerable difficulty There are certain points however, to be constantly borne in mind Osteoarthritis seldom occurs before the fifth decade The patient is usually overweight The joints principally involved are the knees spine and hip and the arthritis remains localized and is in no way migratory There is no periarticular swelling except that Heberden's nodes are practically always present The x rays show bony lipping of the margins of the joints There is seldom any deformity or ankylosis The serological and blood examinations are negative All these features are the opposite to what is found in rheumatoid arthritis There is however, no reason to be dogmatic that either one of these lesions is present alone as it is not unusual for signs of osteoarthritis to develop in later years in a case of rheumatoid arthritis

The varying quality of the joint lesions in rheumatoid arthritis is often a source of much confusion To substantiate the diagnosis there must also be present evidence of a systemic disorder such as unwarranted fatigue accelerated sedimentation rate atrophy of the skeletal muscles weight loss and general debility Psychic factors are at present difficult to assess but their presence constitutes an important phase in this disease which the future must unravel

Prognosis—The prognosis as to life is good but the progress of the disease to a disabling state is always problematical Many cases do not proceed beyond the initial stages while in others it is a steady progressive disability The presence of an increased sedimentation rate, and of specific streptococcal agglutinins are indicative of continued activity while their approximation to normal is indicative of improvement

Treatment—The treatments in the past for rheumatoid arthritis have been almost innumerable and as would be expected most of them have been entirely useless An important development of the recent investigations and study of this disease has been to place the therapy on a more rational basis If it be a chronic infection or the result of a chronic infection it would seem reasonable that it should be treated along the same lines as tuberculosis Therefore such a plan of action should be instituted early in the disease In fact the time is long overdue when this problem should be attacked after the same manner as tuberculosis and institutions for its rational treatment be established such as were advocated for acute rheumatic fever (see page 67) General bodily rest and the avoidance of fatigue are of prime importance, as is also an adequate diet rich in vitamins There are those who consider certain restrictions of diet of importance particularly the limitation of carbo

hydrates but as *rheumatoid arthritics are usually underweight and anemic* dietary restrictions must be carried out with great caution as they may defeat the general plan of supportive treatment A high vitamin diet is best attained by giving cod liver oil yeast and fruit juices in maximum amounts

The removal of focal infections was enthusiastically followed some years ago In fact the removal of these seemed to assume a greater prominence than the treatment of the patient and the arthritis As in all chronic diseases the patient must be placed in the best possible state of general health, and part of this is the removal or correction of focal infections in fact this applies to those in good health as well as to invalids On the other hand ruthless removal of suspected teeth tonsils gallbladders and appendices can be carried out to a harmful degree and furthermore the time should be carefully chosen for such procedures They should not be undertaken when the arthritis is in a *period of acute exacerbation* and if *extensive removal of focal* infections is required this should be done in stages rather than to subject the patient to an exhausting ordeal

Specific and nonspecific protein therapy have had their periods of popularity *The principal substances used in nonspecific foreign therapy* have been typhoid vaccines milk and milk products Much of the former enthusiasm has now been replaced by a more rational scepticism It is true that in active stages temporary improvement may be expected The severe and sometimes dangerous reactions and other unpleasant features from the patient s point of view hardly justify their use Specific foreign protein therapy in the form of vaccines rests on a more rational basis The principal vaccines employed have been prepared with hemolytic streptococci and at one time these were given intravenously with—as would be expected—frequent *severe general reactions which simulated the reactions of nonspecific* protein therapy If vaccines are to be used it is most important that general reactions should be avoided as otherwise although they may be followed by a temporary improvement in many they aggravate the condition or may precipitate an exacerbation This is also true of all foreign protein reactions The subcutaneous administration of streptococcal vaccines should be adhered to if they are to be given at all and should follow the general principles of tuberculin therapy that is the initial doses should be minimal It is best to start with a dosage of about ten million streptococci and gradually increase by one half *this number every four days It is better to be cautious than to* run the risk of producing general reactions The vaccine should be continued for many months or until it is certain that the patient has developed a definite resistance to it If no improvement is then apparent it should be discontinued The invasion by clinicians of the realm of immunology of the principles of which they are pathetically ignorant is no credit to the science or even the art of medicine

In addition to the general bodily rest and rational life the affected joints themselves should not be neglected They should be placed by means of plaster of Paris shells in a position which will relieve all strain upon the joints These should be worn particularly at night During the daytime regular courses of passive movements and in time active exercises should be

instituted, but as long as the joints are in an acute stage, activity should be avoided. Such treatment requires meticulous attention upon the part of the knowledgeable physician, and if success is to be attained, absolute discipline should be required of the patient. On the other hand, immobility to the extent that the joints become "frozen" should be avoided. There is a happy mean between the ankylosis of disuse and too early active movements. A hazard which is too often neglected is that of phlebothrombosis with the risk of pulmonary embolism which may result from prolonged immobility of a limb. This can be avoided by posture and frequent simple massage to assist venous return in the affected part.

Physiotherapy, both local and general, has had its enthusiastic supporters. It should be used by all means but with a reasonable appreciation of what it may attain. There are numerous spas where various forms of this therapy are carried out. It is done in these institutions under strict supervision, and there is no doubt that considerable improvement, although sometimes unfortunately of a temporary character, is often obtained. The use of heat, both locally and in producing artificial pyrexia, has been much employed of late. The former may be accomplished by hot baths, electric light baths or the immersion of joints in solid paraffin with a low melting point. All of these measures may produce local hyperemia and comfort. Artificial pyrexia induced by diathermy and other measures would appear to simulate the effects expected from foreign protein therapy and so far the results have been on a par with this, although the reactions are under better control.

Drug Therapy.—Many drugs have been employed in the treatment of this disease but no conspicuous success has resulted. Any apparent improvement results from the relief of pain and therefore the most popular are the salicylates and allied compounds. These may be given in the form of aspirin to the amount of 40 grains a day but should not be used to the neglect of other therapy. Gold therapy has its enthusiastic advocates. There is no evidence to indicate that it is a specific and its use is frankly empirical. However from reported cases about 60 per cent of cases seem to be improved by its use but of these about 50 per cent have a relapse either following or during treatment. This therapy should be started cautiously with gradually increasing amounts but the maximum should not be more than 50 mg. of the gold salt (50 to 60 per cent gold) once a week. Regular checks of the hemoglobin, leucocytes and nonprotein nitrogen should be carried out. The continuation of a maintenance dose of 25 mg. every fortnight is recommended. Anemia should be combated with iron while periodic blood transfusions are of great benefit. The use of highly concentrated vitamin D in enormous doses has also a present vogue. There is here a real danger unless the therapy can be controlled by frequent blood calcium determinations and the dietary calcium strictly supervised (see page 806). The author has seen three deaths from hypervitaminosis in this treatment (see Figs. 316 and 317).

The lowered surface temperature and sweating, particularly of the limbs with the persistent pain led Rowntree and Adson to employ sympathetic ganglionectomy and ramisectomy in the hope of producing changes in the

vasomotor control of the extremities and so increase the local blood supply This was rewarded with gratifying results in certain of the more chronic and refractory cases Operations for the reduction of contractures and subluxation may at times be required in chronic and neglected cases

Reiter s Disease

Reiter in 1916 described a syndrome characterized by purulent urethritis chronic polyarthritis and a conjunctivitis He claimed it was caused by a spirochete and called it *spirochetosis arthritica*

The onset is usually with a urethritis which is not venereal in origin and the causative agent has not been determined The spirochetal origin is not accepted

Although the triad mentioned above is usually present this is not necessarily the case In addition skin lesions sometimes occur in the form of a keratodermia and Levring has reported prolongation of the auriculoventricular conduction This diffuse distribution of lesions would suggest a systemic dissemination of the causative agent

The course of the disease tends to be chronic with remissions and exacerbations The eventual outlook is good as to life but occasionally keratitis and iritis may lead to permanent ocular injury while the joints rarely are disabled

There is no known treatment chemotherapy and antibiotics are useless

Palindromic Rheumatism

In 1944 Hench and Rosenberg reported a recurring form of arthritis *which they called palindromic rheumatism This was characterized by a recurring* nonsuppurative arthritis without febrile or other systemic manifestations The onset was sudden with pain swelling redness and impaired function of one or many joints The reaction would indicate involvement of both the arthritic and periarthritic tissues It would last for a few hours to several days as rapidly disappear and recur at shorter or longer periods over many years There was no permanent joint disability but it cannot be said that the condition was ever cured The cause has never been ascertained but the whole course and local character of the lesion strongly suggests an *allergic reaction The treatment is symptomatic to relieve pain* Morphia and allied drugs should never be prescribed although they may be given occasionally by the physician

Osteoarthritis

The application of the term arthritis to this condition is hardly justifiable as it is really an arthropathy

Etiology —The cause is not known but there are a number of factors which might seem to enter into its production It is a degenerative lesion and *runs closely parallel with other conditions* which are influenced by age The patients are usually overweight and the joints principally affected are those which would be subject to static or other trauma such as the spine hips

knees and fingers It is also found frequently in those engaged in heavy occupations Perhaps the most important single factor is a familial predisposition

Symptoms —The onset is insidious and the condition is often recognized accidentally in x rays taken for other purposes The symptoms are few and develop when the exostoses or eburnations affect the movement of the joints There are seldom any local signs unless the exostoses reach such a magnitude as to be palpable, although crepitation may be felt and heard but is usually painless The x ray picture reveals bony lipping and spurs along the margins of

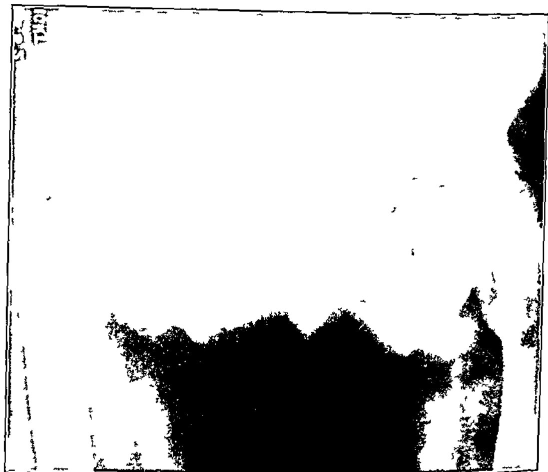


Fig 4 6 —X ray showing morbus coxae senilis of both hips

the articulations In advanced cases there may be rarefaction in the metaphysis and a narrowing of the joint space and changes in shape, although the articular surface remains well defined The most common form of this disease is the so called *Heberden s nodes* which appear in middle life in the terminal phalanges and are most common in women It is seldom that they are painful or interfere with movement although occasionally this may be the case

There now is considered to be an association between this osteoarthropathy and lesions of the cartilaginous structures of the joints A good example is the occurrence of spurs or exostoses at the vertebral margins in cases of herniation of the *nucleus pulposus* The same may be found in the cir

tilaginous components of the knees hips and occasionally the shoulder ankle and elbow In *Malum coxae senilis* (see Fig 456) as an example the principal feature is a destruction of the joint cartilages both of the acetabulum and the femur and eburnation around the periphery of the former In the spinal lesions these may *be difficult to detect before pronounced symptoms and signs* indicative of pressure upon the spinal roots have developed The diagnosis and therapy of these spinal lesions have now become an important department



Fig 45 —Lateral x ray of the lumbar spine in a case of osteoarthritis Note the bony outgrowth indicated by the arrows

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The principal feature in this form of arthropathy is pain which may radiate along the distribution of the spinal roots and nerves as for instance in lesions of the hip the pain may radiate down the thigh and lead to suspicion of a lesion of the knee joint Those of the spine may be called sciatica low

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back pain, lumbago, or other indefinite syndromes This signifies the importance of a detailed examination by x ray and other means to reach a factual diagnosis upon which will rest a rational therapy

There is a group of cases of osteoarthritis which are thought to be associated with the menopause There is little evidence to suggest that this is more than a coincidence, as osteoarthritis usually appears earlier in women than in men, and as at this time there is often a rapid increase in weight, and as the fifth decade is the period when the lesion is most commonly manifest, it is not at all surprising that this correlation suggests itself The knees are most affected and many of these women have a faulty posture (high heels and bad shoes) and flat feet are common The vertebrae and feet are also frequently involved, but other joints may be affected The *symptoms* are those already described for osteoarthritis, and the x ray appearances are identical The *course* of the disease is insidious and continuous, and although it may be arrested, regression never occurs

Senile or senescent arthritis is merely a form of osteoarthritis It is principally found in the spine, fingers, and the larger joints of the arms and legs It is indistinguishable from other forms of osteoarthritis except that it develops in the later decades

Osteoarthritis of the spine, or *hypertrophic spondylitis,* as it is sometimes called is also a form of the same disease in which the principal bony changes are found in the vertebrae It may give rise to considerable limitation of movement It is otherwise symptomless unless the exostoses produce nerve pressure The pain in these conditions has a spinal distribution Very severe and agonizing pain may suddenly occur if through a sudden violent effort one of these exostoses is broken loose It is surprising at times what a slight degree of muscular exertion may produce this Other joints are usually also involved, especially the hips and knees

Anatomical Changes —The anatomical changes in osteoarthritis are purely degenerative, there being a progressive absorption and production of bone which leads to the distorted and irregular ossification about the joints This is produced and aggravated by trauma either direct or from faulty posture The joint cavity itself is practically never involved

Course —The course is extremely insidious and although true ankylosis does not occur locking of the joint may result from impingement of the exostoses

Treatment —The treatment is principally confined to the protection of the involved joints This protection consists of the avoidance of trauma and also in exercises which will improve the faulty posture A reduction in weight in those who are obese is important to accomplish these ends and therefore the patient should be placed on a subcaloric diet Thyroid extract potassium iodide, high vitamin diet and numerous other therapeutic procedures have been advocated, but their effects are to say the least doubtful Pain in the affected joints is often relieved by physiotherapy and particularly local heat Massage and passive movements are to be used cautiously to avoid producing additional local trauma The role of infections was at one time overempha

sized and promiscuous removal of supposed focal infections carried out There is no doubt that these should be removed to promote the well being of the patient rather than for any influence their removal will have on the course of the bony degeneration

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CHAPTER XVIII

DISEASES OF THE URINARY SYSTEM

By Walter de M. Scriver, M.D.

Introduction

The diseases of the urinary system in the strict sense of the term should include all those abnormalities of structure and function which may be present from the glomerulus to the meatus, but from the point of view of the practice of medicine they are usually confined to lesions of the kidney and its pelvis which have an important influence upon the body as a whole. The more local lesions of the urethra, bladder and ureters are dealt with in textbooks on urology. Normal renal function plays an important part in the maintenance of the internal environment, and any interference with its function produces widespread signs and symptoms. In fact many important diseases of this organ may be first suspected rather from systemic symptoms than from the local ones. Therefore it is important for a proper conception of renal diseases that its place in the general function of the body should be appreciated, rather than the narrower view of considering the organ and its functions as a separate entity. The examination of the urine gives important information as to the local anatomical changes occurring, but to assess its functional capacity general results must be investigated.

The anatomical and physiological unit is the nephron, which in its simple form consists of a long tubule, the upper end of which is invaginated by a leash of arterial capillaries (the glomerulus), the lower end of the tubule communicates with the collecting tubules, which in turn empty into the renal pelvis. The glomerulus is closely surrounded by an epithelial layer (Bowman's capsule) which is the invaginated portion of the tubule. As the blood flows through the glomerular capillary, it is thus brought into close contact with the membrane of the capsule through which it is secreted or filtered. (Present day theories favor filtration.) The amount and composition of the filtrate are thus dependent upon the amount of blood passing through the glomerulus, the pressure of blood within the glomerulus and the osmotic pressure of this same blood. It is obvious that the state of the glomerular membrane itself will have a direct influence upon filtration. The filtrate has a composition similar to that of blood plasma minus the protein, whereas in the urine finally discharged from the kidney the individual substances may be concentrated to many times this original strength; thus concentration (and possibly actual secretion) takes place in the tubules which also resorb water. All glomeruli are not in action at the same time, leaving a large reserve to meet extra strain.

The function of the kidney thus in the final analysis depends primarily upon the glomerulus which furnishes the filtrate, and secondarily upon the

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Symptomatology

While extensive disease of the kidneys may exist without giving rise to symptoms there are nevertheless certain symptoms and signs the presence of which may be of significance The most important include changes in the rhythm and volume of urination hematuria albuminuria edema headache pallor dyspnea nausea and vomiting twitching and convulsions and changes in acuity of vision

Changes in Rhythm and Volume of Urination—*Frequency and Polyuria. Frequency refers to the number of times the bladder is emptied* Except for habit spasm it is symptomatic of irritation of the renal pelvis or the bladder either from inflammation or other disease or from distention In the absence of pathological irritation frequency is obviously closely related to the volume of urine secreted Polyuria as its name implies refers to an increase in total volume this may be associated with increased ingestion of fluid either as a voluntary effort or in diseases such as diabetes mellitus or diabetes insipidus In renal disease *polyuria* has been explained as an attempt to excrete the waste products in dilute solution when the kidney has lost the ability to concentrate Nocturnal frequency associated with nocturnal polyuria is suggestive of diabetes or renal disease rather than of a local lesion in the lower urinary tract

Oliguria apart from mechanical causation is the result of decreased glomerular filtration due to any of the general or local causes discussed above

Hematuria is significant of bleeding at any point along the genitourinary tract As a rule the blood from glomeruli or tubules is intimately mixed with the urine which is voided giving it the smoky appearance long known to clinicians In nephritis it is indicative of glomerular damage which allows the leakage of red blood cells into the lumen of the tubule

Albuminuria (Proteinuria)—Though the proteins of the urine consist for the most part of albumin the term albuminuria is actually used in the broader sense of proteinuria Albuminuria apart from that due to the presence of gross blood in the urine is evidence of an increase in the permeability of the glomerulus and Bowman s capsule to the larger protein molecules This may be due either to circulatory or to inflammatory factors Broadly speaking albumin is not a normal constituent of human urine though it may appear in normal people after heavy exercise or effort or sudden changes in circulation such as those caused by a cold bath

Casts occur in the urine for the most part under conditions similar to those associated with albuminuria originating in the kidney their base is thought to be of an albuminous nature In general blood casts and epithelial casts are associated with acute infections granular casts with less acute stages and hyaline casts with the chronic state

Pus cells in the urine are evidence of inflammation in any portion of the urinary or genital tract

Edema—Edema is that condition in which there is present an excess of fluid in the tissue spaces within which it is relatively free to flow under the influence of gravity it tends to collect in the lowest portions of the tissues The process

tubules which work it up into the finished product excreted as urine Generally speaking if the glomerulus fails, all the rest of that nephron fails also

The functions of the kidney in general are

1 To eliminate water } So preserving the salt and water balance
2 To eliminate salts }
3 To eliminate the waste products of nitrogenous metabolism
4 To assist in maintaining the acid base balance of the organism

It is obvious that the secretion of urine may be influenced by numerous extrarenal factors, thus there may be a great decrease in volume when the body becomes dehydrated as from lack of fluid intake, or from loss of ingested

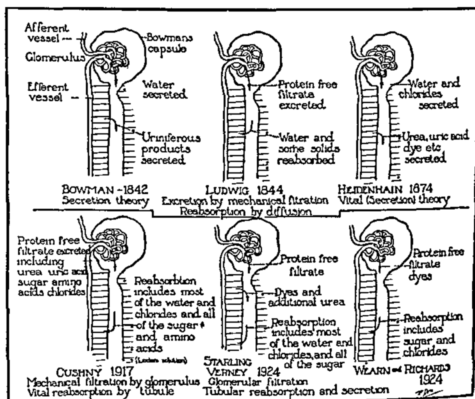


Fig 4 8—Schematic representation of various studies of renal physiology (P S Hench J A M A July 1926)

fluids in the sweat or vomitus or by diarrhea With a failing circulation the pressure or blood flow within the glomerulus may fall to such a level as to be insufficient for filtration (this rarely occurs except in shock) in cardiac decompensation the added factors of asphyxia and tissue imbibition enter the picture Extrarenal factors may also be responsible for changes in the osmotic pressure of the blood

The intrarenal factors will fall roughly into three main groups—those changes which affect the circulation in the glomeruli such as thrombosis, diffuse or focal, changes in the epithelium of Bowman's capsule interfering with permeability, injury to the cells of the tubules below the glomerulus It is evident that there may be a combination of several of these factors

their original concentration In human subjects this edema is seen in those conditions in which the total plasma proteins have fallen below the "critical level" from chronic loss as in repeated hemorrhage long continued serous discharges or massive albuminuria from insufficient protein intake as in dietary deficiency chronic diarrhea or other processes interfering with absorption or from chronic lesions which interfere with plasma protein formation

As the albumin molecule exerts a much greater osmotic pressure than does the globulin molecule losses of albumin are of greater significance and a low level of albumin in the plasma is apt to be associated with edema

As would be expected in a systemic process, the edema produced by this means is generalized and clinically is usually severe and of the "feather bed" type It too may be most prominent in the soft parts and is apt to be associated with transudates in the serous cavities The edema fluid will have a low protein content in contrast to that found in the first type of edema

It is obvious that under certain conditions the ingestion of excessive amounts of fluids may cause edema through a similar process Also the osmotic pressure may be built up in the tissues by salt retention and particularly by the sodium ion in which cases the flow of fluid will again be from the vessels into the tissues While the adrenal cortex appears to be a factor in the control of the sodium balance our knowledge is not sufficient to explain the mechanism in this type of reaction

It is doubtful if the third factor (increased hydrostatic pressure) ever acts alone to produce edema in the human body but it is found frequently in combination with the other two mechanisms A good example is the edema of the feet that comes on after long standing Here asphyxia and interference with drainage of the tissue spaces also enter into the mechanism The protein content of edema of this type will be influenced by the other factors.

Passive Edema —The edema of poor drainage is bound up with the state of the capillaries and lymphatics and the venous blood flow Anything tending to interfere with these will tend to produce edema Pure passive edema is rare in practically all instances one or more of the active factors enters into the condition as well

Other symptoms related to the *uremic state* are discussed below

Tests of Renal Function

With the better understanding of the physiology of the kidney it has become possible to devise tests which will show the total ability of the kidney to carry out its functions In general these tests fall into one of two main groups

1 The ability to excrete water and to concentrate normal products of excretion

2 The elimination of foreign substances

I Concentration and Dilution Tests —In its simplest form this principle has been made use of clinically for many years in the examination of the night and the day specimens Under average normal conditions the night urine will be of a dark color and have a specific gravity above 1 020

may be divided into active and passive forms in the former there is an increased flow of plasma, or of certain of its constituents, from the vessels into the tissue spaces, in the latter the mechanism for the drainage of these spaces (via the lymphatics) is impaired

The active causes fall roughly into three main groups

1 Increased permeability of the vessel wall due to direct injury of the wall (The fluid "leaks" into the tissues)

2 Increased permeability of the vessel wall due to decrease in the osmotic pressure of the blood with corresponding decrease in the force holding the fluid within the vessels (The "thinner" fluid is drawn into the tissues)

3 Increased hydrostatic pressure in the vessels of the region involved (The fluid is forced into the tissues)

As a rule it is rare to find clinically an edema due to a single factor alone, usually at least two, and often all three of the factors are concerned



Fig 459 —Photograph of a patient with the nephrotic syndrome to demonstrate general anasarca Note the edema of face limbs and genitalia and protuberance of the abdomen with pouting of the umbilicus from ascites

A good example of edema due to injury of the vessel wall is that produced by certain snake (viper) venoms in which the capillaries become so permeable that the fluids of the blood escape in large quantities into the tissues Anoxemia also will produce this effect probably through changes in hydrogen ion concentration and cellular permeability In acute glomerulonephritis the causative factor is as yet unidentified being vaguely classified as toxic

Edema of this first type is usually diffuse in distribution and most severe in the soft parts where the histological structure permits a free distention of the tissues Such tissue is found particularly about the skin of the eyelids and the external genitalia

As might be expected the protein content of edema fluid of this type is relatively high, averaging 1 per cent or more

Edema of the second type can be produced experimentally in animals by the process of repeated plasmapheresis in which the blood is withdrawn and freed of the plasma proteins, the cells salts and fluids being reinjected in

their original concentration In human subjects this edema is seen in those conditions *in which the total plasma proteins have fallen below the "critical level* from chronic loss as in repeated hemorrhage long continued serous discharges or massive albuminuria from insufficient protein intake as in dietary deficiency chronic diarrhea, or other processes interfering with absorption or from chronic lesions which interfere with plasma protein formation

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the day specimen may be paler, and the specific gravity may be above or below that of the night specimen This fact has been employed in more elaborate form in many ways

A The Two Hour Test (Modified Mosenthal Test) —In brief the patient eats three ordinary meals but restricts the fluid intake to a total of 500 c c (two glasses) with each meal, no more fluid being allowed during the 24 hours of the test From 8 A M to 8 P M of this day the bladder is emptied *completely* every two hours and the volume and specific gravity of each specimen are determined All urine passed from 8 P M up to and including 8 A M next day is collected as a single specimen Under normal conditions this night volume should not exceed 400 c c, and the specific gravity should be a minimum of 1 020 The individual day specimens should vary in volume, the total being about 800 c c, and the specific gravity should vary eight or more points ranging around 1 020

With failure of renal function, the volume of the night specimen increases and the specific gravity decreases, when the latter is under 1 020, there is always a suggestion of impairment of renal function In extreme renal failure the specific gravity of the individual specimens becomes fixed around 1 010, a sign of grave import In acute renal failure the specific gravity may be low at first, rising with the resumption of secretion In oliguria due to circulatory failure, with a normal kidney, specific gravity will be high ranging around 1 030

B Volhard's Concentration and Dilution Test arrives at these results by withholding food and fluid from the patient after the evening meal until the next morning when he is made to drink 1 500 c c of water Urine is collected hourly for the next four hours during which time the normal kidney will excrete a dilute urine with a specific gravity as low as 1 001, and a total volume of approximately one liter No further food or fluid is given, and further specimens are collected as voided during the day By evening the volume should be low, and the specific gravity should have reached 1 025 or higher With failure of renal function there is inability both to dilute and to concentrate the urine the specific gravity of all specimens ranging closely around 1 010 in those cases in which little normal renal tissue remains

A specific gravity of 1 010 to 1 012 is at the same level as that found in the plasma after the proteins have been removed which suggests that urine of this fixed specific gravity is but a dialysate produced by a kidney which has completely lost its power of concentrating the urine, a function of the tubules

In both of these tests it is obvious that if the patient should happen to be excreting edema fluid at the time of the test, or should take extra fluid by mouth, the results will be fallacious These sources of error should be watched for carefully in all tests

Urea Concentration and Clearance Tests —As urea is a normal constituent of the urine it has been made use of as an index of the ability of the kidney to concentrate Ambard's original formula has now been generally superseded by more modern versions In *MacLean's concentration test* 15 grams of urea dissolved in 150 c c of water is given to an adult in the fasting state after

the bladder has been emptied The urine is then collected at hourly intervals for two hours Provided that the volume of the second specimen is not greater than 120 c c a normal kidney should excrete a urine containing a minimum of 2 per cent of urea If the urea content of a blood sample taken at the end of the second hour be determined Addis concentration factor can be determined by the ratio

$$\frac{\text{Urea per cent in urine}}{\text{Urea per cent in blood}}$$

In a normal individual the factor should be above 35 and more usually 40 or above

In *Van Slyke s urea clearance test* the patient may have breakfast and no urea is given During the course of the morning two consecutive hourly specimens of urine are collected and a single blood specimen is taken before the end of the second hour From these the "standard" and "maximum" clearances (blood "cleared" of urea) are calculated according to the urea content of blood and urine and the volume of the latter Results are expressed as percentages of normal (maximum 75 c c per minute where volume of urine is above 2 c c per minute and standard 54 c c per minute where volume of urine is below this amount) according to the following formulae

1 Maximum clearance (per cent of normal) $\frac{100}{75} \times \frac{UV}{B}$

2 Standard clearance (per cent of normal) $\frac{100}{54} \times \frac{U\sqrt{V}}{B}$

II Excretion of Foreign Substances —Of all the tests based on the excretion of foreign substances the best known and most widely used is the phenolsulfonphthalein test often known as P S P or red test In this case 6 mg of the dye (1 c c of the solution supplied in ampules) is injected into the lumbar or gluteal muscles and after ten minutes has been allowed for absorption specimens of urine are collected over the next two hours These urines are then made strongly alkaline diluted to a given volume and the colors are compared with a standard The result is considered to be normal when from 60 to 85 per cent of the dye is excreted in two hours of which 40 per cent or more is passed in the first hour In extreme renal insufficiency only a trace of dye may be present

Blood Chemistry —Increase in the blood of those substances normally excreted by the kidney may give strong indirect evidence of renal insufficiency Of the nitrogenous products the total nonprotein nitrogen should not exceed 35 mg per 100 c c by the original Folin Wu technic Urea nitrogen should not be greater than 16 mg per 100 c c Creatinine is the last of the nonprotein nitrogen substances to increase and any rise in the level above the upper normal limit of 1 5 mg per 100 c c should always be considered significant Similar levels however may be found in high intestinal obstruction

U = Mg per 100 c.c. of urea in urine.
B = Mg per 100 c c of urea in blood
V = Volume of urine per minute in c.c.

As a decrease in the concentration of proteins in the plasma may be a factor in the production of edema the determination of this level may be of importance A total plasma protein below 5 per cent is usually associated with edema, particularly when the decrease has been so predominantly in the albumin fraction as to cause a reversal of the normal ratio of approximately 1 5 of albumin to 1 of globulin As the level of cholesterol usually runs inversely to that of the proteins, an increase in this substance above the upper limit of 200 mg per 100 c c may also be of significance

In advanced chronic renal insufficiency there may be an increase in the inorganic phosphorus of the serum, coincident with a decrease in the calcium If the total proteins are low, the calcium may also be low due to decrease in the fraction bound to protein, but the inorganic phosphorus is usually found within normal limits

TABLE XVI

COMPARISON OF FUNCTIONAL TESTS IN DIFFERENT RENAL STATES

	RELATIVELY NORMAL KIDNEY IN A CASE OF SIMPLE HYPERTENSION		GLOMERULONEPHRITIS WHICH HAS PASSED THROUGH THE NEPHROTIC STAGE		ADVANCED GLOMERULONEPHRITIS IN UREMIC STATE	
Two hour test	VOLUME C.C	SPECIFIC GRAVITY	VOLUME C C	SPECIFIC GRAVITY	VOLUME C C	SPECIFIC GRAVITY
8 to 10 A M	150	1 010	80	1 015	4[illegible]	1 008
10 to 12 A M	[illegible]0	1 018	[illegible]	1 017	[illegible]0	1 010
12 to 2 P M	145	1 008	8[illegible]	1 01[illegible]	1[illegible]	1 010
2 to 4 P M	70	1 016	100	1 01[illegible]	9[illegible]	1 010
4 to 6 P M	40	1 022	70	1 01[illegible]	70	1 010
6 to 8 P M	40	1 024	100	1 01[illegible]	220	1 010
8 A M to 8 P M	495	1 008 1 024	500	1 01[illegible] 1 01[illegible]	605	1 008 1 010
			455	1 01[illegible]	[illegible]50	1 008
8 P M to 8 A M	[illegible]0	1 024				
Urea concentration and factor	2 [illegible]% 43 4		1 [illegible]0% 22 2		Not done because of extreme urea retention	
Urea clearance (Standard)	82 0%		[illegible]8 0%		8%	
Phenolsulphonphthalein (Two hours)	80 0%		3[illegible] 0%		Traces	

BRIGHT S DISEASE

Bright s disease is a somewhat general term which includes that disease group in which the kidney is the seat of progressive changes of vascular and inflammatory nature which changes are but special local manifestations of a more generalized process occurring in the body as a whole It does not include the ordinary suppurative processes in the kidney nor tuberculous or syphilitic infections but corresponds to the clinical entities included under the term nephritis '

Classification—The many classifications proposed have been the most potent source of the general confusion which has reigned in this field The first grouping used was on a basis of morbid anatomy such a classification is responsible for the terms large white kidney etc Later an attempt was made to classify according to the clinical symptoms and so we have such

descriptive phrases as chronic nephritis with (or without) edema, etc In many cases there appears to be little agreement between the two The better understanding of the physiology and pathological physiology of the kidney has served to make things more clear particularly so if we remember that the morbid anatomical specimen is merely a fixed point (the end stage) in a continuous clinical process which has led up to this point

The clinical features which are used for classification are edema hematuria and nitrogen retention It is obvious that it will not be uncommon for two of these symptoms to be associated in the same case and all three may be present on occasion

In general in relation to the pathological picture we find hematuria and nitrogen retention occurring where the glomerular lesion is the outstanding feature and edema when the tubule appears to be the most affected portion Table XVII is an attempt to correlate some of the various classifications which have from time to time been put forward

TABLE XVII

CLINICAL	CLINICOPATHOLOGICAL	CLINICOPATHOLOGICAL	PATHOLOGICAL
(Acute) hemorrhagic	(Acute) glomerulonephritis	Acute nephritis	Acute exudative (hemorrhagic) nephritis
Chronic nephritis with edema	Chronic nephrosis	Chronic diffuse nephritis	Large white kidney
Chronic nephritis with edema	Nephrotic state of glomerulonephritis	Chronic mixed nephritis (diffuse and interstitial)	Large → small white kidney
Chronic nephritis	Chronic glomerulonephritis	Chronic interstitial	Small white kidney
(Chronic) hemorrhagic Chronic hypertensive	Chronic glomerulonephritis	Chronic interstitial	Primary contracted kidney Small red kidney

Etiology —Clinical observations and experimental researches would suggest that there may be several factors which may be responsible for the development and progress of a nephritic process these fall in general into three main groups bacteria and their toxins certain chemicals and progressive vascular changes

Of the bacteria associated with nephritis the most common is the streptococcus its primary focus frequently is in the throat as in tonsillitis and scarlet fever though it may flourish elsewhere Staphylococcus (from skin infections) and pneumococcus are less frequently concerned While the colon bacillus is found frequently in pyelitis it is practically never directly concerned in the nephritic process

The present tendency is to ascribe the local renal changes to an allergic response of the kidney to the infecting organism rather than to direct implantation of the organisms in the glomerular loop such as actually occurs in the focal nephritis of subacute bacterial endocarditis In diphtheria where a severe acute glomerulonephritis may arise the process is due to the diphtheria toxin Chemical nephritis is usually due to poisoning accidental or suicidal by some of the heavier metals of which mercury is by far the most common The renal lesion in these conditions does not resemble patho

logically that found in any of the other clinical types, and if the patient lives long enough, the kidney lesion heals completely

The vascular lesion which initiates the nephritic process may be secondary to an infection or toxin, or to the ordinary wear and tear phenomena which proceed in the vascular tree with increasing age The role of focal infections in the production of nephritis is still not completely proved, such effects as might be ascribed to them have been mentioned above under bacterial and toxic factors

The Experimental Production of Nephritis

Early attempts to produce nephritis in animals were all made by the administration of chemicals which have a direct toxic action on the kidney, those most used include mercury, uranium, and cantharides The lesions produced in these experimental animals differ little from those which result in human subjects from toxic doses of the same drugs but in no case has there been any great similarity either in the complete clinical picture or in the pathological findings to those processes seen in human subjects suffering from Bright's disease

A condition of the kidneys which resembles closely, both in its clinical course, and in the pathological changes in the kidney, the chronic glomerulonephritis which occurs in human Bright s disease has been produced by Hartmann, by exposing the kidneys of experimental animals to varying doses of x rays These results are of great importance in stressing the essentially *vascular* nature of the process

The so called nephrotic ' state has never been produced in animals by any experimental measures which result in a pure renal lesion With the introduction by Leiter of the process of plasmapheresis whereby the plasma proteins can be reduced sufficiently to upset the osmotic pressure relations of the blood we are now able to produce at will in the experimental animal a massive edema which in practically all respects resembles that found in the nephrotic state without of necessity having an associated renal lesion

Smadel has produced nephritis experimentally in animals by the injection of nephrotoxins These have been prepared by immunizing an animal of species B to extracts of kidney of species A and then injecting into an animal of species A the immune serum B so produced Similar results cannot be produced if the immunizing extracts are prepared from organs other than the kidney The severity of the nephritis thus produced varies directly with the size of the dose of immune serum

It is of interest that, despite the apparent relationship of glomerulonephritis to streptococcal infections attempts to produce an experimental nephritis by using injections of this organism have failed to give consistent results

Glomerulonephritis

With the exception of certain chemical nephritides practically all nephritis is at some stage a glomerulonephritis From the anatomical point of view this means interference with the blood supply of the glomerular loop, and the

convoluted tubules and from the physiological side implies an interference with the filtration process *through the glomerulus and probably the secretion* process in the convoluted tubules also It is thus obvious that the extent of renal insufficiency will be directly proportional to the degree of involvement of the individual glomerulus and the number of glomeruli affected As the outstanding pathological lesion is in the glomerulus so the outstanding clinical sign is hematuria Associated signs may be those related to a general vascu*lar lesion such as hypertension changes in the ocular fundus* and in some cases edema

Acute Glomerulonephritis

(Acute Hemorrhagic Nephritis)

The onset of this condition is frequently sudden during the course of an acute infection such as tonsillitis or pneumonia or some days after the apparent subsidence of the infection

In many cases the patient awakens with swollen eyelids and face, and soon becomes edematous in all the loose tissues The edema is apparently of the first type (discussed above) and may be so extreme as to close the eyelids completely In the acute stages it is not usual to find fluid in the body cavities

Coincident with the development of the edema there is an oliguria or actual anuria which may persist for several days Such urine as is passed is dark in color and definitely bloody or with lesser amounts of blood smoky in appearance Unless there has been previous failure of renal function the specific gravity is relatively high and albumin is present usually in large amounts On microscopic examination numerous erythrocytes are seen many of which occur in the form of red blood cell casts coarsely granular and epithelial casts may also be present and leucocytes in numbers varying with the acuteness of the inflammatory process

Further Clinical Features —Unless there has been previous cardiovascular disease the heart is not enlarged The blood pressure however in the acute stages is increased and may at times reach approximate levels of 200 mg Hg systolic and 120 diastolic The larger blood vessels show no signs of sclerosis or thickening but in the early stages occasionally the arteries of the fundus oculi can be seen to be greatly constricted while the veins are relatively full in extreme cases hemorrhage and exudate may be present There *may* also be a generalized contraction of the smaller vessels of the skin which assumes a pale appearance suggestive of anemia the blood examination however may give a normal hemoglobin and erythrocyte count though the leu*cocytes may be increased*

The nonprotein nitrogen elements of the blood vary more or less directly with the degree of oliguria in complete anuria they may rise rapidly to high figures to subside more slowly as the urinary output increases

The acute stage may vary from a relatively small hematuria with little edema to an acute anuria with massive edema it may be very short in duration with rapid subsidence and complete cure or may have a more gradual remission of symptoms with either complete cure or progress into the chronic state In a certain number of cases the acute stage terminates in death within

a few days of the onset, this is more common in cases associated with diphtheria With the remission of the oliguria large volumes of urine are secreted resulting in the subsidence of the edema The hypertension gives way to a normal blood pressure level, and the ocular fundus resumes a normal appearance *Complete cure is not uncommon in children, but such* a fortunate result is less frequent in adults in whom the subacute or chronic forms usually follow Blood may continue in the urine in microscopic amounts for some days or weeks after the subsidence of acute symptoms Its protracted appearance, however, is always highly suggestive that the condition has entered into the subacute or chronic stage

As this condition progresses there is a gradual loss of renal function, often without symptoms until the well marked chronic stage is reached

Chronic Glomerulonephritis

Clinically this type is distinguished by progressive failure of renal function and increasing nitrogen retention with the symptoms related to this state Anatomically the outstanding feature is the progressive destruction of the glomeruli and tubules with replacement by fibrous connective tissue which causes gross shrinkage of the organ eventuating in the terminal stage of 'small white (or red) kidney" (primary or secondary contracted kidney)

The etiological factors of this condition may be many or unknown, as stated above it may result from the continuation of acute glomerulonephritis, on the other hand it may appear quite insidiously with no recognizable preceding acute stage or infectious process This type of renal lesion may be associated with the gouty diathesis or with chronic lead poisoning, occasionally it appears to follow on an apparently simple ' hypertension Numerous attempts have been made to implicate excess protein diet, and particularly meat, as an etiological factor but clinical observation and experimentation have failed to bear out the results sometimes obtained in animal experimentation While the chronic form may appear at all ages the majority of cases occur in later life particularly those with an insidious onset

In the later stages the symptoms of both the so called primary and secondary forms are similar In the early stages there are relatively few symptoms the persistence of albuminuria and particularly hematuria, may be the only finding to draw attention to the progressive feature of a once acute glomerulonephritis The accidental discovery (as in examination for life insurance) of albuminuria may be the first sign that the "primary" process has begun

In the early stages the most significant symptoms are those associated with the secretion of urine With the decrease in actively functioning renal tissue, there is impairment in the ability to concentrate the waste products which are thus of necessity excreted in more dilute solution in the urine In consequence it will take a larger volume of urine to keep the excretion of solids up to the necessary daily level and so polyuria and frequency result As a rule *the first increase is voided in the night urine* which becomes progressively a larger fraction of the total 24 hour amount, at the same time the

specific gravity of the urine becomes lower in all specimens until ultimately it becomes fixed at a specific gravity of 1 010 to 1 012 which represents a simple protein free plasma filtrate with no attempt at concentration

The albumin content of the urine may at first be relatively large in amount, but as the disease progresses it decreases, and in the end stages may be merely a trace, though dilution may account for some of the decrease yet the total *quantity is also decreased* Microscopic examination will always reveal red

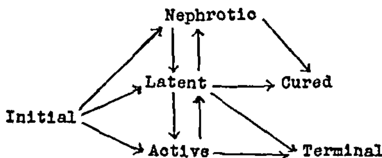


Chart XXXI.—Diagrammatic scheme of progress of glomerulonephritis modified from Addis

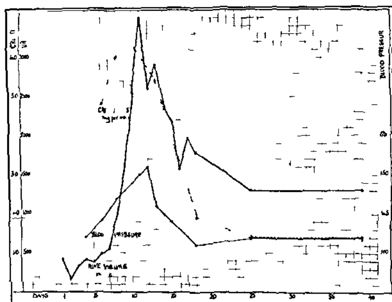


Chart XXXII —Chart showing rapid retention of creatinine in acute anuria and return to normal with diuresis

blood cells though they may be very few in number particularly in the late stages Casts at first are mainly of the coarsely granular and cellular type as the disease progresses they become more finely granular and ultimately are principally of the hyaline variety Occasionally gross hematuria occurs associated with a flare up of the chronic into an acute or reactivated phase of glomerulonephritis In this case unless there be a large amount of blood the specific gravity of the urine remains relatively low

The level of the nonprotein nitrogen in the blood varies inversely with the ability of the kidney to concentrate In the early stages it is within normal limits, but gradually it begins to increase from its level of 25 to 35 mg per 100 c c until in late stages *it may reach as high as 200 mg per 100 c c* Of the individual substances the urea is the first to increase, and reflects slighter degrees of failure than does the creatinine which is the "last to go up" and when increased is evidence of severe renal failure As the condition approaches the uremic state, the inorganic phosphorus of the serum begins to *increase associated with* a concomitant decrease in serum calcium

Early in the process clinical symptoms may be absent, with the progress of the disease, apart from those definitely referable to the urinary tract (uremia), they fall into the groups referable to circulatory system and toxic changes

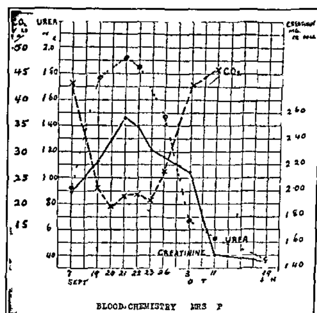


Chart XXXIII —Graph showing retention of urea and creatinine with associated acidosis in acute exacerbation of chronic nephritis with recovery of function

Edema, which may be so prominent in the acute form usually does not appear until late and then in the dependent parts as it is referable to general circulatory failure Occasionally there may be a slight puffiness about the eyes while the disease has still some of the acute features but this stage does not persist for long

Hypertension develops relatively early in the process and continues throughout at first the systolic phase alone may be affected but later the diastolic level also rises the pulse pressure usually remaining fairly high Coincidentally the thickness of the vessel wall increases (as found in the smaller arteries such as the radial) the thickening being more in the muscular coats and not of the calcareous plaque type met with in advanced arteriosclerosis With the hypertension enlargement of the heart ensues chiefly of the "left sided" type A systolic murmur may be heard due to relative mitral insufficiency In some cases a fibrinous pericarditis develops as a terminal phenomenon

In the retina there may be mild or advanced changes frequently the onset of visual disturbances is the first sign that draws attention to the true nature of the disease In general the condition varies from early vascular changes to actual hemorrhage and exudate, and swelling of the disc Although there has been a tendency to formulate the rule of death within two years of the onset of albuminuric retinitis, yet in individual cases there has been a complete clearing of the retina and slow progress of the renal condition

As the disease progresses an apparent exophthalmos develops which may even suggest Graves disease, but the pallor of the skin is in distinct contrast to the flushing seen in that condition

The progress of the disease may be extremely slow, extending over years or it may run a fatal course within a year or so of the onset of the first symptoms the ultimate termination is in uremia unless this event is anticipated by cerebral hemorrhage or thrombosis or cardiac failure, or by some fatal intercurrent infection

Nephrosclerosis

This term has been applied to that form of renal lesion in which the change is primarily in the afferent artery of the glomerulus rather than in the glomerular tuft itself The symptoms are gradual in onset and often the first indication that the disease is present is the finding of albuminuria and hypertension at a routine physical examination Unlike glomerulonephritis there is no history of infection at the onset and it also appears in later life usually from the fourth decade on The clinical story of hypertension and renal failure is similar to that of chronic glomerulonephritis While this is the small red kidney of the pathologist as opposed to the small white kidney' of glomerulonephritis yet on occasion it may be impossible to diagnose the etiological factor from the morbid anatomy and histology alone and the clinical history is necessary to give the final diagnosis

The Uremic State

True uremia (literally urine in the blood') may be defined as that symptom complex which results from the retention within the organism of those substances which are usually eliminated in the urine These include water inorganic salts nitrogenous waste products and certain organic substances It will thus be evident that there may be several toxic factors and so the uremic state may express itself in several ways Pseudouremic symptoms may be produced by local edema or circulatory changes in the brain arising either independently of or associated with the retention of toxic products, but it is now a generally accepted rule that there can be no true uremia except where renal function has so failed that nitrogen retention can be demonstrated in the blood

This failure of renal function can be acute as in the case of sudden destruction or removal of the kidney tissue or chronic where the destructive process has gone on for months or years

Uremia has been produced experimentally in animals by surgical removal of both kidneys thus preventing the formation of urine by the ligation of

both ureters, producing a similar effect slightly more slowly, and by damaging the kidney by poisons All of these methods produce an acute uremia, which is not the type usually seen in clinical medicine More recently the modern means of producing experimentally true progressive nephritis (x ray radiation) have succeeded in producing chronic uremia (see experimental nephritis)

The symptoms are not due to urea *per se*, for large doses of urea can be given such as will raise the urea in the blood to levels seen in the uremic state without producing similar symptoms Likewise, other well known substances, such as uric acid and creatinine, have been shown to be relatively innocuous If the total nonprotein nitrogen of the blood be determined in a normal individual and the nitrogen of all known nonprotein nitrogen substances be determined at the same time, it will be found that the sum total of the latter is not as great as the former, this difference representing unidentified substances is called the "rest nitrogen" As nitrogen retention proceeds, with increasing amounts of nonprotein nitrogen in the blood, this rest nitrogen increases at a much greater rate so that in extreme retention it represents a large fraction of the total There has been a natural tendency to consider that in this moiety is the substance—or are the substances—which account for the uremic syndrome

It is also of significance to note the similarity of the symptoms occurring in hepatic failure to those seen in uremia indeed, at times they are liable to lead to mistaken diagnoses The liver is an organ of detoxication and excretion, among other functions and failure of these functions results in the retention of toxic products (See page 727) A finding in uremia that suggests a link between the two conditions which as yet has not been satisfactorily explained is the occurrence of a positive van den Bergh reaction in the serum of uremic patients

Symptoms and Signs of Uremia

The majority of the symptoms and signs are due to irritation or depression of the central nervous system though they may manifest themselves in other organs both reflexly or directly The most common symptoms are discussed below

Disturbances of the Sensorium — *Apathy stupor*, and *coma* are usually produced by retained toxic substances especially the phenols, which depress the higher centers The patient is drowsy and not interested in his surroundings, yet he will usually respond quite rationally when questioned, relapsing into the drowsy state when conversation ceases Except in the terminal stages coma is rare

Restlessness and *irrational states* obviously must be explained by a different mechanism here the cause is a poor circulation, from local vascular changes, or a generally failing circulation with the production of a mild degree of oxygen lack in the brain tissues

Visual Disturbances —Often these are the first symptoms noted by the patient They are commonly due to vascular lesions in the retina which have

been discussed above (page 1269) These lesions may also occur in "pure" hypertension without renal disease and in the pre uremic state and so are not necessarily "true" uremic signs, they are however, usually present when the uremic state has set in

Headache is commonly present, and is usually ascribed to "toxic" products, *but, it is often due to increased intracranial pressure associated with* edema of the brain and particularly the meninges In the former case the pain is dull and nagging, rarely acute and uninfluenced by posture, pain due to edema is usually more severe and is influenced by posture The headache of pure hypertension is commonly worse in the morning wearing off as the day advances the uremic headache is present most of the time

Motor Phenomena—Muscular twitchings are frequently present in the slowly progressing *chronic uremic states and are practically never seen in* those uremias which are of acute onset They are usually seen as sudden contractions of individual muscles or muscle groups which follow no definite pattern and do not include purposeful movements All reflexes are usually increased when twitchings are present

These evidences of muscle irritability have been attributed to the low level of calcium in the blood plasma The total serum calcium is frequently found to be low in the "nephrotic" state as well where no twitchings are observed whereas they may be present with a similar serum calcium value in uremia This apparent discrepancy is explained by the level of ionised calcium in the nephrotic state it is normal whereas the amount of calcium bound to the plasma proteins is reduced because of the decrease of the latter in the uremic state the plasma proteins are usually at a normal level with a normal amount of "bound" calcium whereas the ionised calcium is decreased This decrease in ionised calcium is directly dependent upon the increase in the plasma of the inorganic phosphorus associated with renal insufficiency

It will be noted that the explanation of muscle irritability is reminiscent of that of tetany (see page 961) and so it is not surprising that the school *that would ascribe the symptoms of tetany to guanidine should also account* for those of the uremic state by an increase of guanidine in the blood due to failure of excretion The chemical evidence for this however is not very strong

Convulsions are probably rarely if ever due to toxic factors but to edema of the brain or local circulatory disturbances in such cases they are not primarily "uremic" However as both circulatory failure and edema are so frequently present with the toxic retention convulsions have usually been considered as expressions of the uremic state They are usually severe and epileptiform in nature they may be single or multiple

Dyspnea may be due to associated circulatory failure when it is apt to be paroxysmal and nocturnal if more severe periodic or Cheyne Stokes *breathing may be a prominent feature* The dyspnea of "pure" uremia is due to acidosis associated with the retention of such acid radicles as chloride phosphate and sulfate and the loss of fixed base that occurs from failure

of the ammonia forming function of the kidney, and from loss of base in vomitus The CO_2 combining power may reach such low levels as 10 volumes per cent

This dyspnea is of the Kussmaul type, with strong and deep expiratory phase (For further discussion of dyspnea see pages 323 to 331)

Vomiting may be a very distressing symptom and at times may make it impossible for the patient to retain nourishment taken by mouth Its causes are usually "toxic," operating by several mechanisms (1) The vomiting center may be directly stimulated, (2) there may be local irritation of the gastrointestinal mucosa from ammonia formed by the breakdown of urea which is at high concentration in the tissues and is excreted into the gastro intestinal tract In this respect it has long been held that the frequent finding of ulceration of the stomach intestines and particularly of the colon at autopsy in this type of case is produced by a similar mechanism combined with local infarctions due to terminal vascular paralysis Occasionally diarrhea occurs, due to the colitis so produced

Loss of weight and general wasting are present in all cases of chronic uremia though they may be masked by edema The obvious cause of the undernourishment is the lack of sufficient caloric intake and absorption, due in turn to several factors of which anorexia nausea and vomiting are the most important With the lack of sufficient fluid intake the patient may become extremely dehydrated In addition to the evidences of this state seen in the skin and subcutaneous tissues, the tongue is dry and beefy in appearance Acute parotitis, probably due to infection spreading up the ducts from the mouth is a not infrequent terminal complication which precedes death by but a few days

Pallor is practically always present It has a dual origin (1) actual anemia which has been shown to be due to a depression of the bone marrow (2) a smaller vascular bed due to "shutting down" of the capillaries of the skin with a consequently smaller amount of oxyhemoglobin per unit of area to color ("Pale hypertension" of Volhard)

Ecchymoses are frequently found on the limbs less frequently on the body and rarely on the face They are due to increased permeability of the vessel walls, terminal vascular paralysis and changes in the blood itself caused by the retention of toxic products

Epistaxis is frequent from infarction and ulceration of the nasal septum The bleeding point usually is easily found on the septum not far from the external opening of the nares and is better treated by local styptics or cauterization than by diffuse pressure

Occasionally skin irritation occurs as an intractable pruritus This has been ascribed to the formation of ammonia from the urea which is excreted in the sweat and deposited as a "frost" on the skin where it decomposes

The Nephrotic Syndrome

Probably no division of Bright s disease has caused so much controversy or confusion as that classified under the head of "nephrosis" The original diagnosis was based on a purely pathological viewpoint and referred to the

condition in which the tubules alone appeared to be affected, the glomeruli and blood vessels being free By far the majority of cases are of the mixed type, that is, both clinically and pathologically they show evidences of the nephrotic and glomerulonephritic state The author is of the opinion, along with many others that the so called 'pure' nephrosis is relatively rare and that if many cases so diagnosed were only followed carefully for a sufficient length of time evidences of glomerulonephritis would ultimately be found To avoid confusion we shall first discuss the so called *pure* nephrosis

The etiology is uncertain, frequently there is a history of an antecedent infection of the upper respiratory tract in many cases *there has been malaise* often with fever which has been diagnosed clinically as influenza or grippe Infection of the paranasal sinuses was much stressed at one time as the actual cause In the majority of cases however it is difficult to find a definite etiological factor

The outstanding clinical features are edema and heavy albuminuria At the onset the edema is usually slight beginning in the feet and gradually extending up the legs later it develops into a general anasarca with soft pitting edema over the whole body including the face and a large amount of fluid in the serous cavities The swelling of the genitalia may be so great as actually to render urination extremely difficult the fluid in the serous cavities may give rise to respiratory and cardiac embarrassment This edema usually develops slowly in contrast to that found in acute glomerulonephritis and *may persist for months At times it may disappear rapidly*, but as a rule the subsidence is a slow process As already stated, there is a massive albuminuria though this is the urine which is familiarly reported to 'boil solid" yet the actual protein content rarely exceeds 2 per cent The specific gravity is usually close to 1 020 and in the microscopic examination no red blood cells are found though casts are present in variable numbers The casts include granular and hyaline types and rarely cellular varieties if the polarized light be used many are seen to contain doubly refractive globules which also may be present free in the urine these are the lipoids which Munk feels are specific of the disease process

The blood serum is milky in appearance as originally described by Bright There is no nitrogen retention but the total protein content of the plasma is lowered the loss being almost wholly in the albumin fraction due either to impaired formation or/and to urinary protein loss This lowering of the plasma colloids is the chief cause of the massive edema as discussed above In addition there is a large increase in the cholesterol in the blood and a lowering of the calcium due to decrease in that portion bound to the proteins

In the pure nephrosis these comprise the total abnormal clinical findings The heart blood vessels and blood pressure are normal the fundi show no changes in the vessels and no hemorrhage or exudate though there may be some edema of the retina

The various tests of renal function give good results and the whole picture is more one of water retention in the tissues than of renal failure Epstein has called the condition diabetes albuminuricus' and ascribes the

of the ammonia forming function of the kidney, and from loss of base in vomitus The CO_2 *combining* power may reach such low levels as 10 volumes per cent

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may develop while the edema is still present and the patient may even have an increasing systolic blood pressure and nitrogen retention at this time Ultimately the edema regresses and the picture is that of advanced glomerulonephritis as outlined above, with none of the features typical of the nephrotic state

It must be borne in mind that death may take place at any stage in the procession of events, and so the actual picture in the kidney can vary from "pure" nephrosis with much tubular degeneration and lipoid infiltration but relatively normal glomeruli to the secondary contracted kidney as discussed above Many patients die of pneumococcic peritonitis

Intercapillary Glomerulosclerosis

In the chronic diabetic whose condition has been inadequately controlled over several years there may develop a clinical picture which closely resembles that of the nephrotic state characterized by edema often massive in extent albuminuria hypoproteinemia hypertension and retinal lesions of varying degrees of severity The condition progresses with increasing nitrogen retention and usually ends in uremia within a year or two of the onset of symptoms unless a vascular accident anticipates this ending

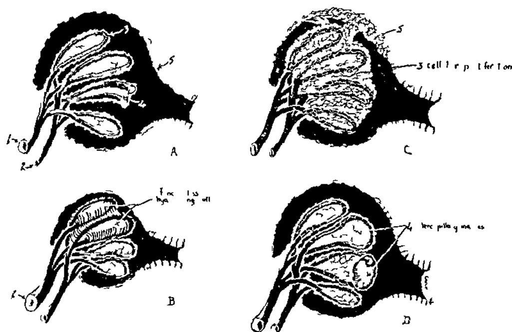


Fig 460 A diagrammatic representation of the location of the lesions in certain renal disorders

A Normal glomerular structure and circulation (1) afferent arteriole (2) efferent arteriole (3) glomerular capillary tuft (4) intercapillary masses (5) Bowman's capsule

B Arteriolar nephrosclerosis Note the *primary* lesion in the afferent arteriole (1) which is a thickening of the wall and narrowing of the lumen to eventual obliteration with consequent functionless hyalinized tufts

C Glomerulonephritis Note that the lesions in the glomerular capillary tuft (3) and Bowman's capsule (5) ... cellular proliferation and adhesion with eventual degeneration of both structures

D Intercapillary glomerulosclerosis Note that the lesion is in the intercapillary masses (4) leading to eventual compression and obliteration of the glomerular tuft (Courtesy of Dr Sydney Freeman)

sequence of events to a primary loss of proteins in the urine through some *little understood metabolic upset, with relatively little renal disease*

An interesting feature of many of these cases is that their *basal metabolic* rate runs at a low level a rate which is still low even when allowance is made for the edema weight It requires large doses of thyroid substance to produce any effect in raising the rate During the active process the patient is more *susceptible to infections*, particularly by the pneumococcus, which not infrequently sets up a peritonitis in the ascitic abdomen as a terminal complication

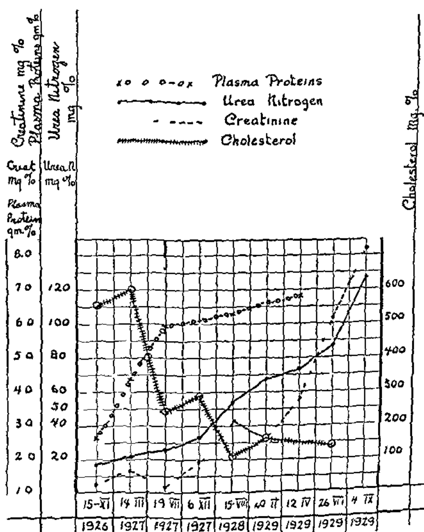


Chart XXXIX —Composite curve of blood urea and creatinine plasma proteins and cholesterol over a period of three years showing change from the nephrotic state to that of severe nitrogen retention

By far the majority of these cases of nephrosis occur in children in whom the disease may frequently proceed to complete healing with gradual or rapid loss of edema *ultimate* clearing of the albuminuria and restoration of the blood to the normal chemical state On the other hand a large number of apparently pure nephrosis cases ultimately take on the signs of *glomerulo* nephritis as evidenced by the findings of red blood cells in the urine the gradual increase in blood pressure and changes in the fundi These signs

assimilated With both milk and fruit juices the total fluid intake should be watched and adjusted to the occasion This regime will be found much more acceptable to the patient than the so called " thirst cure " and usually gives equally as good results

In the stage of acute oliguria no attempt should be made to supply more fluid than is necessary to replace that lost through the skin lungs and digestive tract As a general rule the average adult may be given each day a *total volume equal to the urine output of the previous day plus 1000 c c* If vomiting should be severe this amount should be increased correspondingly Diuresis cannot be forced by loading the body with fluid which it is unable to excrete and such extra fluid in the tissues may actually do harm by producing edema of the brain and other vulnerable tissues

Chlorides should be replaced in accordance with the loss of this ion in the vomitus sweat and other fluids in any prolonged state of oliguria the daily determination of the chloride level in the plasma is almost an essential in *determining proper treatment*

The addition of glucose in 5 or 10 per cent concentration to the fluid given intravenously will serve to supply an available carbohydrate as a source of nourishment

With the subsidence of the acute stage, more solid articles of diet can be added such as cereal milk and milk puddings toast, cooked fruit baked or mashed potato Later the higher protein foods can be added Chicken fish, and meat have relatively similar protein content and according to recent *observations, have little injurious effect on the kidney even in acute stages* As chicken is relatively more bulky a given weight will appear much larger to the patient than the corresponding weight of red meat

With the chronic or subacute stage a more permanent dietary regime can be instituted On the whole the tendency in the past has been to cut the protein intake too drastically with insufficient intake the body proteins may break down leading to loss of weight and adding to the nitrogen available for urinary excretion If the protein deficit be spread over a long period *actual depletion of the body reserves and finally of the plasma proteins may* follow so inducing the nephrotic state and its associated symptoms

Thus there can be no hard and fast rule for diet in chronic cases the protein intake should be varied to fit the individual case When there is no marked increase in the nonprotein nitrogen of the blood it may be sufficient to restrict the protein by allowing a small serving of chicken fish *or* meat once daily to limit eggs to one a day and milk to not more than one glass a meal Cheese as a high protein food may be used as a substitute for egg or *meat one cubic inch of the yellow domestic variety is the equivalent of* one egg or half a meat serving In the presence of an advanced degree of nitrogen retention the protein content of the diet should be reduced to the minimum Often this is achieved automatically by the patient s symptoms but where it is not a diet of the type suggested for the acute stages is more suitable

High protein diet is indicated in the nephrotic syndrome when the plasma proteins are at a low level To obtain a high intake which should average

The lesion found in the kidney is distinctive as first described by Kimmelstiel and Wilson, in the nature of a fibrous tissue proliferation between the loops of the glomerular capillaries leading gradually to a complete replacement of the functioning glomerulus and loss of the corresponding nephron

Vascular Renal Failure

The kidney requires a good circulation of blood in order to carry out its function Experimentally any interference with outflow from the renal vein will tend to produce a heavy proteinuria, if long continued, or severe, casts and even red blood cells may appear in the urine

In circulatory failure if the kidney be relatively normal, these same factors hold The volume of urine is decreased, such as is secreted has a high specific gravity (about 1 030) contains a fairly large amount of protein and casts, usually of the granular variety red blood cells are rare In severe cardiac failure there is frequently a moderate rise of the nonprotein nitrogen in the blood values as high as 60 mg per 100 c c are not uncommon, these return to normal limits as the circulation improves and more urine is excreted Creatinine values however rarely exceed normal limits

Frequently the question may arise as to whether we are dealing with a circulatory failure, secondary to chronic renal insufficiency, or with a primary circulatory failure with secondary renal manifestations In these cases the specific gravity of the urine is all important, the badly damaged 'chronic" kidney cannot concentrate urine, and so no matter how great the circulatory failure, the specific gravity of the urine still remains low (approximately 1 010 to 1 015) on the other hand, the normal kidney will respond to the circulatory failure by concentrating the urine to the high levels of specific gravity mentioned above In very acute renal failure, the specific gravity may be high, but many red blood cells and leucocytes will be found in the urine

Treatment of Nephritis

Preventive measures must of necessity be very general in nature These include the avoidance of exposure to the elements and to infection and the proper care of any infection once initiated A warm climate with no sudden changes of temperature is most advisable but as very few patients can afford to move to such a region if they do not already live there they should be protected against the variations of the weather This is best carried out by wearing woolen underwear, which will absorb perspiration and prevent chilling ' in winds or after exertion as it can be procured in light weights for hot weather it may be worn the year round Similarly wet feet damp shoes and stockings, etc should be guarded against and changes to dry clothes made as soon as possible

Diet —In acute nephritis with oliguria or anuria, the general principle is to give a diet which is easily assimilated contains little or no nitrogen and has a relatively low salt content the fruit juices answer these requirements best, and are usually most acceptable to the patient Despite its widespread use, a pure milk diet is not theoretically as useful, as it contains approximately 3 per cent of protein and a relatively large amount of salts, and is not so easily

Edema.—Appropriate treatment obviously demands a diagnosis of the causative factor and measures directed toward its alleviation or cure.

For the edema associated with acute glomerulonephritis, the so called thirst cure has been recommended. In the strict form no fluids are given until urinary secretion has been resumed, a procedure which involves great suffering by the patient; in a less severe regime the fluids are cut down rigidly to an absolute minimum of varying amount. With the resumption of secretion a diuresis usually results which clears the body of the excess edema fluid and the intake can be correspondingly increased.

The edema of the nephrotic syndrome is usually extremely resistant to treatment, yet frequently spontaneous improvements occur which have no apparent definite relation to any of the therapeutic measures in force at the time. In general it is wise to balance the fluid intake against the output; as the urinary excretion is low, a 24 hour intake of 800 to 1000 c.c. (approximately 4 to 5 glasses) is usually sufficient. (See also the Schemm regime above.) In theory a high protein diet is indicated as outlined above. If repeated analyses of the blood are made the nonprotein nitrogen will often be seen to rise after the high protein diet has been taken for some time. This should not necessarily be taken as a sign of increased renal failure unless the creatinine also is appreciably elevated. An increase in nonprotein nitrogen alone is frequently seen and is probably due to the split products of the food proteins in transport to the process of building up the specific body proteins. This diet must be continued for many weeks before the proteins will be restored to normal levels. Salt restriction has been discussed above. Occasionally a change of diet to one composed of fruit juice or milk will give a greater general restriction of both fluids and salt than has previously been obtained.

The use of diuretics should be considered carefully for each individual case, with particular care for those which are direct renal irritants. Urea will occasionally produce sufficient diuresis to reduce edema. Obviously it will be useless in those cases where there is already a considerable urea retention in the blood. In other cases it should be given in sufficient dosage to produce a "head" in the blood stream, e.g., 5 grams or more every 3 or 4 hours for five doses.

The acid producing salts occasionally are useful in initiating diuresis though as a rule they are apt so to irritate the stomach as to induce vomiting. Ammonium chloride 1 gram in water every hour for six doses is usually sufficient to produce an effect if it is to be obtained. This drug can now be obtained as an "enteric coated" tablet.

The mercury diuretics such as salyrgan, neptal, etc., have been advocated in the nephrotic state, particularly in combination with the acid producing salts. In the author's opinion drugs of this type are dangerous in practically all types of Bright's disease and if they are used daily urinalysis and microscopic examination should be made so that signs of renal irritation may be observed at an early stage and the drug be discontinued before severe damage is done.

Because of the low basal metabolic rate that is frequently found in the nephrotic state thyroid and thyroxin therapy have been used. These patients

125 grams of protein or more daily, will necessitate the use of meats fish eggs cheese and milk in large quantities

Vegetables are relatively low in nitrogen except peas and beans and as nitrogen in these latter is not readily available for body building they are better omitted from the dietary Asparagus gives rise to hippuric acid a possible renal irritant and so likewise it should be omitted Most of the fruits can be taken freely, but as plums (including prunes) and cranberries give rise to benzoic acid also a possible renal irritant they are better omitted from the diet While the ordinary cereal products contain proteins, their use in moderation is permissible On general principles it is wiser to omit rich puddings and pastries The use of spices should be discouraged as there is sufficient reason to believe that these substances may be irritating to the inflamed kidney Pepper, mustard catsup, etc, are obvious sources less obvious are some of the candies, or soft drinks such as ginger ale which may contain very little ginger but an appreciable amount of capsicum a definite renal irritant

Although salt is not properly a spice, it is usually considered with the condiments When edema is present it is wise to restrict the salt intake, as the sodium ion is the one which helps hold water in the tissues Even in the nephrotic state where there may be a relatively good excretion of salt ingested its restriction often favors the excretion of greater amounts of fluid from the body stores with a corresponding diminution in edema This principle is the basis of the treatment advocated by Schemm who prescribes a salt free diet and at the same time forces water intake even up to 10 liters daily While many cases of edema notably those of cardiac type (see page 367) improve under this therapy yet a truly salt free diet is most unpalatable and can rarely be prepared outside a special diet kitchen However if free salt be forbidden at the table and only a moderate amount be used in the cooking favorable results may be obtained The use of salt substitutes will thus be unnecessary Several of these have excluded the chlorine ion but still retain the sodium ion which is the one more intimately concerned with water retention Closely related to this type of treatment is the so called rice diet which has been brought forward by Kempner principally in the treatment of hypertension Its chief value would appear to be in its low sodium content but it soon becomes monotonous and is not adapted to long continued treatment

Soups are usually a great source of salt in addition to their high content of nitrogenous ' extractives if they have been made from meat stock As none of these has any food value and the path of excretion is through the kidney the exclusion of ' clear' soup from the diet would seem logical Simple purees however with no base of stock may be allowed

Tea coffee and cocoa all contain some of the xanthin diuretics which act by direct irritation of the renal epithelium their use therefore becomes undesirable on general grounds However if the patient appears to suffer from their deprivation he may be allowed one cup of weak tea or coffee at a meal The use of substitutes must be considered according to the merits of the beverage and the patient s desires

Convulsions—Convulsions if severe must be treated by the administration of strong sedatives such as chloral hydrate by rectum or sodium amytal intravenously The use of chloroform by inhalation is not advisable if it can be avoided Where the convulsions are related to edema of the brain, the intravenous injection of 10 c c of a 25 per cent solution of magnesium sulfate may be very efficacious, in such a case a 10 per cent solution of a calcium salt such as the gluconate should be ready for immediate injection in case of magnesium shock Equally good results, without the danger of shock, can be obtained by the use of intravenous injections of hypertonic sugar solutions, the usual amounts given are 100 c c of a fifty per cent glucose solution, or 150 c c of a twenty five per cent sucrose solution

The twitchings seen in the course of uremia are usually more annoying to the members of the patient's family than they are to the patient Because of their relation to the diminution of ionised calcium in the blood it would seem logical to give calcium intravenously, as in the form of a ten per cent solution of calcium gluconate The results, however are disappointing as the amount of ionised calcium changes very little in the presence of the hyperphosphatemia

The Artificial Kidney

All of the procedures outlined above have been in the ultimate analysis attempts either to restore kidney function or to reduce the concentration in the tissues of those products of body catabolism which the kidney is failing to excrete

From the consideration that the kidney is in general a dialyzing membrane there arose the concept that other semipermeable membranes of the body might be made to act vicariously Accordingly there was developed the procedure of peritoneal lavage at first intermittent later continuous with favorable results in some cases Such a method has obvious limitations many difficulties and is not without danger

The principle of actually dialyzing the patient's blood against Ringer's or other solutions has recently been developed to a point where the artificial kidney is now a recognized therapeutic instrument With this type of treatment many grams of nitrogenous and other waste substances can literally be washed out of the blood stream and tissues after a few hours of treatment the high nonprotein nitrogen of the blood can be reduced to a normal level The whole procedure in practice is complicated and requires trained personnel to carry it out but it may be the means of saving a life in cases where the renal failure is of a temporary nature from which the patient can recover if he is not allowed to die of uremia in the meantime

Renal Rickets

This is a form of chronic nephritis which occurs in children in which the features are those of chronic *glomerulonephritis associated with dwarfism* and rachitic changes in the bones The disease begins in infancy or early childhood and may last for several years ultimately ending in death with uremic symptoms or from some intercurrent infection The nephritic symp

are extremely resistant to such preparations and may often require 3 grains or more of thyroid extract daily without showing toxic effects or, indeed much change in the basal metabolic rate

The treatment of the edema of circulatory failure occurring in the course of renal disease should follow the outline presented in that section

Anemia —As a rule the anemia of nephritis is secondary to a depression of bone marrow activity The exhibition of iron in various forms may be followed by some improvement in the blood picture, Basham's mixture has long been a favorite form of administration Blood transfusions have relatively transient effects and are not of great use

Vascular Renal Failure —Here the treatment obviously depends on restoration of the local and general circulation These measures have been discussed elsewhere (see page 364)

The Uremic State —The type of diet that is indicated in this state has been discussed above

Headache —In the early stages headache may be the main symptom If it be due to edema of the brain the measures discussed above for the treatment of edema may give some relief The ' toxic'' headache associated with nitrogen retention may respond to the general measures, or it may be necessary to use added drug therapy Tablets or capsules of the popular combination of acetyl salicylic acid with caffein and phenacetine, and in severe cases codeine, usually will be helpful and unless they are taken in large numbers the theoretical bad effect on the kidney can be neglected Lumbar puncture may be tried in severe cases and frequently affords prompt relief

Vomiting —If vomiting is severe, gastric lavage may give some relief, it is well to remember however, that the gagging and struggling associated with the passage of the stomach tube may raise an already high blood pressure to dangerous levels, in which case the nasal tube may be less objectionable When vomiting is prolonged fluids are best administered intravenously Originally it was believed that hypertonic glucose solutions might 'force'' a diuresis but this has not been borne out in practice The glucose however is a source of energy for the body and if it be given in 20 per cent solution a relatively large amount can be given in a volume which is not too large Frequently an intravenous injection of 300 c c of 20 per cent glucose saline twice daily will make the patient feel much more comfortable

In addition to the above procedures, high colonic irrigation with warm or hot tap water may be tried once or twice daily according to the strength of the patient It is thought that nitrogen elimination by the bowel is encouraged in this way Sweating has fallen into disfavor as its physiological effects are better understood It has been shown that the nitrogen and salt content of the sweat is relatively low the water high consequently the effect of a successful sweat will be actually to concentrate presumably the 'toxic' substances, the nitrogen and salts in the body tissues and blood stream As an edematous patient rarely can be induced to sweat profusely, this method is not of much use in aiding the elimination of edema fluid

Amyloid Disease of the Kidney

Amyloid is deposited in the kidney as in other organs during the course of certain chronic cachectic diseases such as tuberculosis syphilis, and prolonged suppuration

The amyloid kidney may be normal in size or moderately enlarged, and on section appears lardaceous The amyloid is deposited in and about the capillaries and small arteries, as in other organs consequently glomeruli so affected may be destroyed with subsequent degeneration of the tubule

The symptoms are similar to those observed in the nephrotic syndrome with massive albuminuria followed by edema while the loss of protein in the urine is one cause of the lowered plasma proteins, there may also be a poor absorption of proteins in the diet if the intestinal tract is also involved by the amyloid condition, or if diarrhea be a prominent feature prolonged suppuration also causes a considerable loss of protein to the body

Treatment involves the removal of the cause if possible, the attempt to furnish a high protein intake, and the general treatment outlined for the nephrotic state On the whole the prognosis is poor though death may not follow for several years after the onset of renal symptoms

Congenital Polycystic Kidneys

This condition resembles closely in its clinical picture that of advanced glomerulonephritis with its hypertension and vascular changes and signs of renal insufficiency Palpation of a mass in the region of one or both kidneys should always excite suspicion of this condition in the presence of the other signs X ray may be of aid in demonstrating the large kidney mass if palpation is difficult

The majority of these patients die before their fortieth year, though occasional cases may be found later in life The treatment is similar to that outlined for chronic nephritis

Congenital Aplasia of the Kidney

While congenital aplasia of the kidney is not a common lesion yet its occurrence is of sufficient frequency to warrant its consideration as a possible contributing factor in advanced degrees of renal failure

Its presence may be suspected in those cases of Bright's disease (and of surgical conditions of the kidney) in which there is a rapid failure of renal function which is out of proportion to what might be expected from the history and clinical findings The actual diagnosis will depend upon the demonstration of the condition by pyelography or at operation or autopsy

The defect in development is more common on the left side, where there may be either no demonstrable kidney tissue, or a small undeveloped mass of rudimentary kidney tissue the ureter also may be absent, rudimentary not patent or much dilated with or without stricture The condition is perfectly compatible with life and good health as long as the other kidney is normal, but with its loss of function symptoms develop rapidly

The treatment is that indicated for the remaining kidney

toms are similar to those seen in the glomerulonephritis of adults except that hypertension is rare, at least until late in the disease The bony changes are probably related to the upset in calcium and phosphorus metabolism which is found in the advanced nephritic state (see above) Infantilism may be a prominent feature, but as death takes place before puberty or soon after, it is usually not as marked as the other associated conditions The treatment is similar to that outlined for chronic nephritis, modified where necessary to fit the age of the patient

Orthostatic Albuminuria

Orthostatic albuminuria is a condition occurring chiefly in children and occasionally in young adults, in which albuminuria is present intermittently without the presence of renal or urinary tract disease The albumin usually disappears when the patient lies down, and appears when he is in the erect position though to a lesser extent when he is moving about Standing in the position of attention, especially with heels, buttocks, shoulders and head against a vertical surface such as a wall, increases the albuminuria, on the other hand, if while he is standing the patient places one foot on a stool or chair, the albuminuria disappears

All of the positions which produce albuminuria also produce a lordosis whereas the "nonalbuminous" positions tend to correct this posture The production of albuminuria has been explained as due to the pressure of the lumbar vertebrae indirectly on the left renal vein with consequent interference with circulation of a "passive congestion" type By catheterizing the ureters of patients with this condition Sonne has shown in a small series of cases that when albuminuria was present, it always came from the left ureter and never from the right thus lending support to this theory

Diagnosis depends upon finding specimens of urine free from albumin The urine should be passed before rising from bed in the morning, as well as later in the morning The absence of albumin in the first and presence in the second is diagnostic If the specimens of the two hour renal function test be examined for albumin it may be found in some and not in others Occasionally it may be necessary to have the patient empty his bladder and then lie down in a "curled up" posture for an hour or two, voiding at the end of each hour, to obtain an albumin free urine In all cases renal function tests should be carried out they must fall within normal limits to permit of the diagnosis of orthostatic albuminuria The condition occurs more commonly in hyposthenic individuals though it may appear in the robust Casts are present not infrequently

No treatment is necessary though exercise to counteract the lordotic tendency may aid in eliminating the condition The albuminuria *per se* is not of importance Parents should be reassured as to the innocent nature of the condition It may persist for years but usually disappears with the period of adolescence

sacrificed are ones such as the skin and skeletal muscles to be followed by the kidneys and liver and finally the central nervous system lungs and myocardium

This *diversion of the reduced blood volume to parts where it is most essential* is apparently accomplished through selective vasoconstriction The skin and the skeletal muscles would be the first to show evidence of such being the case These tissues can endure profound ischemia and reveal few after effects with eventual complete restoration of function The kidneys *however, cannot stand such a degree of ischemia* and will early show a deficiency of function which may be permanent leading to fatal uremia or it may be reversible depending upon the degree and duration of the ischemia It would seem obvious that there is a deep purpose for the blood supply to the lungs myocardium and central nervous system to be maintained as long as *possible against all hazards The failure of function of any one of them would* lead to early death

It would be impossible to deal with all the various causes of shock as there have now been enumerated somewhat over thirty but we shall take as examples acute loss of whole blood as in hemorrhage plasma loss as in burns and cholera or the simpler dehydration of water and electrolyte loss as in persistent vomiting in all of which there is eventually a grave fall in blood pressure

The first effect on the kidney would be vasoconstriction leading to decreased renal blood flow with a parallel reduction of secretion or oliguria even to anuria In this phase the general blood pressure may for a time be maintained which is part of a defense reaction but this may in a short time also fall There is then a summation of causes leading to renal ischemia If these are not too complete or prolonged and the general circulation is restored renal function will be resumed without permanent damage to the kidney cells It must be appreciated that renal vasoconstriction alone without a low blood pressure may cause a degree of renal failure and if sufficiently prolonged may lead to irreversible renal damage

The brilliant experiments of Trueta and collaborators would indicate that there may be another manner by which renal failure and uremia may be produced after injury They demonstrated that the application of a tourniquet to the *left* hind leg of a rabbit for some hours caused a withdrawal of blood from the *left* renal cortex and a great acceleration of blood flow through the medulla This is revealed by the increase of the total blood flow through the kidney the venous blood being almost arterial in color and the renal vein being *distended and pulsating It was suggested by Trueta that the blood flow* through the cortex was shunted through the medulla thus preventing its filtration in the cortex leading to a cessation of renal function This phenomenon was apparently of neurogenic origin and not comparable to the conditions arising in hemorrhage or traumatic shock In the latter the renal blood flow is not accelerated but greatly diminished and the kidney *continues to* extract 85 to 90 per cent of para amino hippurate from the plasma indicating that such blood as continued to perfuse the kidneys was reaching nephrons of normal excretory capacity

Renal Arteriosclerosis

Up to recent times there was considered to exist a close relation between arteriosclerosis and renal failure. This apparently arose from a confusion of the anatomical lesions resulting from the arteriolar sclerosis of hypertension (primary contracted kidney, page 450), secondary arteriolar changes occurring in the terminal stages of chronic hemorrhagic Bright's disease (secondary contracted kidney, see page 1266), and true arteriosclerosis of the later decades. It is the last group which are at present being considered. The renal arteries usually reveal considerable atheroma and there may be definite infarcts with cystic formation and a general atrophy of the cortex. The effect upon renal function is not at all distinctive and here again it is surprising the small amount of functional disability which may result. In fact the arteriosclerotic kidney cannot be accused of producing any definite clinical pattern. It is true that hematuria may be intermittent, that proteinuria and cylindruria may be found but, serious interference with renal function as represented by nonprotein nitrogen retention etc. is seldom conspicuous, and uremia is rare.

Infarcts of the Kidney

These fall into three main groups, small embolic infarcts, arteriosclerotic infarcts and the massive infarction of bilateral necrosis (lower nephron nephrosis).

Emboli may lodge in the kidney in the course of any septicemic process, if they be relatively large they are accompanied by the usual symptoms of sudden pain (in the loin), shock of varying degree, oliguria and hematuria. These symptoms usually subside in the course of a few days but the episodes may be repeated.

In focal glomerulonephritis the infarcts are small, and involve only a small portion of individual glomeruli. The only symptom may be the presence of hematuria, gross or microscopic. They are common in the course of subacute bacterial endocarditis. Total renal function usually remains unimpaired, and the treatment is that of the general disease, although sometimes the renal lesion is so extensive as to lead to uremia.

Lower Nephron Nephrosis

Tubovascular Renal Syndrome

Grave impairment of renal function, even leading to fatal uremia, has been described following shock due to severe trauma or hemorrhage, crushing injuries, posttransfusion reactions, toxic effects of sulfonamides, arsenic, mercury, carbon tetrachloride and other nephrotoxins, as will be pointed out below. The renal ischemia which may be of a severe degree in shock causes pronounced tissue anoxia which acts in the role of a nephrotoxin.

All tissues are not equally affected by anoxia, for example the skin and voluntary muscles appear to stand long periods of ischemia, while the central nervous system and the myocardium are particularly sensitive and the liver and kidney stand somewhere midway. There is ample evidence to suggest that as the circulating blood volume is reduced, the first tissues to be

and inorganic phosphorus Vomiting may be present, and even severe but there are usually none of the classical symptoms of uremia What urine is secreted is of low specific gravity, contains protein and some *blood cells* and in the early stages heme pigment or heme stained casts may be found There *is no definite pattern to the* blood pressure levels which are essentially low but may rise moderately The oliguria has been reported as lasting as long as nineteen days but unless the urinary secretion is restored early death occurs on the average on about the eighth day

Treatment consists in measures to combat the shock at the onset to restore the circulating blood volume with blood plasma or salt solutions as indicated and to raise the blood pressure level In those cases which follow the transfusion of incompatible blood the *prompt administration of* sufficient alkalies to produce an alkaline reaction in the urine has been thought to be of value Continuous oxygen therapy should be given in high concentration in order to raise the amount in physical solution in the plasma and so help to reduce the tissue anoxia The use of peritoneal lavage or the artificial kidney if available is strongly indicated as it must be appreciated *that the* lesions in many of these cases of lower nephron nephrosis are reversible

Crush Syndrome—In addition to the *nephrotoxic effect of anoxia there* may be additional factors present In this regard the crush syndrome must be mentioned Although scattered references to this condition are found in the literature before 1940 it was as the result of the mass bombing of civilian centers when cases could be followed from the initial injury to the *terminal stages some days later* that attention was *focused upon an old syn*drome with a new title

The name was derived from crushing injuries of soft parts with or without fractures The victim when released was in shock or shortly developed it and it might be fatal or he might recover from this phase and pass into a stage of progressive uremia with hypertension But in these cases there are two features of particular significance namely (1) In the early stages there is an excessive amount of potassium in the urine This is supposed to be derived from the macerated muscle of the crush injury (2) Although in all forms of uremia there may be an increase of the blood potassium in this syndrome with the onset of oliguria the blood potassium continues to rise at an excessive rate until it may reach a level of 30 to 40 mg per cent Myoglobinuria with obstructive casts was supposed by some to play an important role in the renal lesions but now the consensus is that the detritus may only contribute to the progress of the lesions initiated by the ischemia of the initial shock It has been suggested that the phenomenon described by Trueta and mentioned above may account for some cases of renal failure in this syndrome But it would seem necessary in such cases for the crushing injury to involve *both limbs and to have the same effect as a bilateral tourniquet*

It is postulated that the progressive and excessive increase in blood potas*sium is due to its reabsorption from* the tubules in excessive amounts derived from the macerated muscle Death is considered to be due to a combination of uremia and cardiac failure caused by potassium intoxication

This first or ischemic phase may be followed if the shock continues by a second stage where if there is any urine passed, it is of low specific gravity with low urea clearance This would indicate renal damage But the degree cannot be assessed accurately The renal recovery may lag behind the shock and eventually be complete indicating that the anatomical lesion has been reversible On the other hand after the shock has been recovered from kidney function may improve for a while and then fail again indicating progression of the lesion Finally there are those cases where renal failure is progressive indicating permanent and irreversible injury leading to uremia and death

It is difficult to foretell which of these three results may occur The margin of safety is narrow and many patients in severe shock may die before uremia develops On the other hand it is impossible to say which patients would recover if the uremia could be controlled by an artificial kidney or peritoneal lavage in the hope of eventual reversibility

The character of the renal lesions has been extensively studied by Lucke and Mallory in man after battle injuries by Badenach and Darmady in rabbits and by Van Slyke in dogs Although there are some differences as to details in general the findings may be summarized as follows glomeruli and proximal tubules practically undamaged distal convoluted tubules and thick tubules of Henle degenerated and showing necrosis Mallory points out that in the first 24 hours visible lesions do not appear which would indicate that the lesions are aftereffects of damage not histologically demonstrable suffered by the tubular cells during the period of shock

In Lucke s series of 538 cases 403 were subjects of the type of shock mentioned above while 67 cases were due to poisoning caused by substances such as sulfonamides arsenic carbon tetrachloride etc Therefore it would appear that nephrotoxic agents as well as shock produce the same type of lesion He coined the term lower nephron nephrosis' to cover all these conditions

Lucke pointed to the similarity of the findings in shock to those noted by Richards when he studied the effect of nephrotoxic substances such as mercuric chloride on the nephron of frogs This was in brief that the glomerular filtration took place at a normal rate but the entire filtrate was reabsorbed from the tubules In other words the cells of the tubules have lost their normal capacity of selective reabsorption by which they take back from the glomerular filtrate sufficient water to prevent dehydration glucose amino acids electrolytes etc and discard or let the return of urea uric acid creatinine, etc and excess water and electrolytes In Richard s nephrotoxic kidneys the tubules act as a dead membrane and everything passes through and there is anuria

It is true that this process has not been definitely demonstrated in the shock kidney as in Richard s nephrotoxic frogs but it has been shown by experiments in dogs that such kidneys lose most or all of their power to extract para amino hippurate from the renal plasma nor can they concentrate the glomerular filtrate both of which facts would point to a tubular damage

The clinical features include pronounced oliguria or complete anuria rapidly increasing retention of nonprotein nitrogen creatinine potassium

that in cases of infection of the lower urinary tract the infection reaches the kidney by passage through the lymphatics into the blood stream In the lesions of the pelvis, contributing factors are stasis and mechanical injury, as from obstruction and "back pressure"

Symptoms—Certain symptoms and signs are common to all of these infections as they have their origins in the same physiologico pathological processes Pain is due to stretching of the renal capsule or pelvis it is felt in the "back" more definitely in the loin If tenderness be present, it is most acute in the costolumbar angle, though if the kidney be palpable through the anterior abdominal wall it also will be tender Frequency is also dependent reflexly upon irritation of the renal pelvis or the ureter, the micturition may be painful, though if this be a marked symptom disease of the bladder should be suspected Fever is of the type which might be expected in a pyogenic condition where the amount of absorption of septic material is related to the degree of drainage There may be an initial chill often followed by others, *the fever may be mild or intense*, and of the intermittent or remittent type when there is some drainage, continuous where drainage is absent The leucocyte count also will vary with the degree of toxicity and absorption Nausea and vomiting are other systemic symptoms which are related to the degree of general depression of the patient they may be absent Albuminuria of the "febrile" type will be found, but unless the suppurative process takes place in a portion of the kidney communicating with the renal pelvis no pus will be present in the urine In some cases blockage of the ureter below the pelvis will effectually prevent the passage of the pus where pus is present red blood cells are usually found also in microscopic amounts If the inflammatory lesion has been of such a nature as to involve a large amount of the renal parenchyma, there may be a loss of renal function of varying degree with associated signs and symptoms as outlined above

Cortical abscess is most frequently found in association with an existing or preceding furuncle or carbuncle or other staphylococcus infection of the skin or other tissues Symptoms may be vague and merely those of a general infection At times loin pain may be severe but pyuria is rarely a feature *owing to the situation of the inflammatory process in a portion of the kidney* away from communication with the pelvis The infection may spread through the capsule of the kidney into the perinephric tissue forming a perinephric abscess when general symptoms of sepsis will become more severe followed by local edema of the skin over the costolumbar region and swelling in this region

In general septicemia multiple abscesses of the kidney may occur in many cases symptoms and signs are lacking and the lesion is found only at autopsy

Pyelitis—Pyelitis should more properly be called pyelonephritis as the inflammatory process also involves the parenchyma of the kidney to a greater or lesser extent Apart from the infecting organism which is usually the colon (or tubercle) bacillus the chief contributory factor is obstruction to the free drainage of the kidney pelvis as from "kinking" of the ureter in ptosis of

A rational feature in the treatment, in addition to the prevention and reversal of shock and the control of the uremia by the artificial kidney or peritoneal lavage would be to combat the potassium intoxication This may be attained through a proper balance of the fluid used in peritoneal lavage or by the administration intravenously of calcium which is an antagonist of potassium Insulin and glucose have also been advocated

Hepatorenal Syndrome—It has long been appreciated that renal failure may supervene in chronic liver disease and it may also be associated with acute liver lesions such as acute hepatitis or after hepatotoxins like chloroform cinchophen dioxane and carbon tetrachloride It has also been suggested that this may be a prerenal uremia There are, however, cases reported following shock from hemorrhage and burns and more rarely after dehydration due to simple water and electrolyte loss

It has been mentioned above that all organs are not equally affected by the vasoconstriction in shock The liver may follow after the kidney and so hepatic lesions may be less common than the renal On the other hand jaundice is a more obvious sign than is early oliguria In cases after severe postpartum hemorrhage with shock it may be shown that incipient signs of renal failure such as rising N P N lowered CO_2 combining power and oliguria with low specific gravity may precede the jaundice This hepatorenal combination is a particularly dangerous one as the detoxicating power of the liver as well as other important functions are impaired, and this combined with the failure of renal excretion of toxins permits the rapid accumulation of those noxious but unknown substances which make the final stages of hepatic and renal failure so much alike

The treatment of the hepatorenal syndrome is most unsatisfactory It is obvious that the ischemia of shock should be combated by all means It would also seem indicated that the diet should be high in carbohydrate and low in fat The place of protein is still disputed It is a protector of the fatty liver but it may be possible that it is the source of toxic end products which the liver normally detoxicates The use of methionine in 2 Gm (30 grains) doses four times daily has its advocates, vitamin B complex intramuscularly is also recommended while the therapeutic role of choline is still doubtful

Infections of the Kidneys

These include those diffuse and focal inflammations of the kidney parenchyma and pelvis in which we are able to demonstrate a definite bacterial etiology

Etiology—The bacteria concerned fall into three main types 1 The colon group found almost exclusively in infections of the pelvis, rarely where the parenchyma has been the original focus 2 The pyogenic cocci (staphylococcus, streptococcus pneumococcus) which affect the parenchyma of the kidney primarily 3 The tubercle bacillus giving rise to lesions which involve both parenchyma and pelvis and the lower urinary tract

Bacteria reach the kidney through the blood stream or the lymphatics or by retrograde infection of the ureter in cases where the latter has been injured as by obstruction The work of Wallace however tends to show

that in cases of infection of the lower urinary tract the infection reaches the kidney by passage through the lymphatics into the blood stream In the lesions of the pelvis, contributing factors are stasis and mechanical injury, as from obstruction and 'back pressure "

Symptoms—Certain symptoms and signs are common to all of these infections as they have their origins in the same physiologico pathological processes Pain is due to stretching of the renal capsule or pelvis, it is felt in the back,' more definitely in the loin If tenderness be present it is most acute in the costolumbar angle, though if the kidney be palpable through the anterior abdominal wall it also will be tender Frequency is also dependent reflexly upon irritation of the renal pelvis or the ureter the micturition may be painful though if this be a marked symptom disease of the bladder should be suspected Fever is of the type which might be expected in a pyogenic condition where the amount of absorption of septic material is related to the degree of drainage There may be an initial chill often followed by others the fever may be mild or intense and of the intermittent or remittent type when there is some drainage continuous where drainage is absent The leucocyte count also will vary with the degree of toxicity and absorption Nausea and vomiting are other systemic symptoms which are related to the degree of general depression of the patient they may be absent Albuminuria of the febrile" type will be found but unless the suppurative process takes place in a portion of the kidney communicating with the renal pelvis no pus will be present in the urine In some cases blockage of the ureter below the pelvis will effectually prevent the passage of the pus where pus is present, red blood cells are usually found also in microscopic amounts If the inflammatory lesion has been of such a nature as to involve a large amount of the renal parenchyma there may be a loss of renal function of varying degree with associated signs and symptoms as outlined above

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Pyelitis—Pyelitis should more properly be called pyelonephritis as the inflammatory process also involves the parenchyma of the kidney to a greater or lesser extent Apart from the infecting organism which is usually the colon (or tubercle) bacillus the chief contributory factor is obstruction to the free drainage of the kidney pelvis as from 'kinking of the ureter in ptosis of

the kidney, or blockage of the ureter from calculi or external pressure The frequency of right sided pyelitis during pregnancy is ascribed to pressure by the enlarged rotated uterus upon the right ureter

Symptoms and *signs* vary according to the severity of the infection and the degree of drainage possible An initial chill is frequent, and recurrences are also frequent The fever varies in degree, and is accompanied by a rapid pulse The patient may appear quite septic, and delirium may be a prominent symptom Pain and tenderness in the loin is common, not infrequently it may be bilateral, one kidney or both may be palpable Urinary symptoms may be severe and the urine literally 'loaded with pus' so as to be visible macroscopically, the reaction is acid to litmus paper and the urinary volume may be reduced In severe cases it is not unusual to find fine crepitations at the base of the lung on the side of the involved kidney, they clear up with the subsidence of the renal infection

The *prognosis* for acute attacks of pyelitis is good though they may be prolonged and frequently may pass into the chronic state in which acute exacerbations are not infrequent If the lesion has been sufficiently destructive of the renal parenchyma, hypertension and other signs of renal failure may supervene

Tuberculosis of the Kidney—No attempt will be made to discuss this condition in detail for a fuller description the reader is referred to any standard textbook of urology

As a general rule renal tuberculosis is unilateral in situation except in advanced cases The primary lesion is in a papilla whence it spreads until ultimately it breaks through into the renal pelvis, giving rise to symptoms The process of spread in the kidney follows the same general rules as in other organs

Tuberculous infection of the pelvis gives rise to the same local symptoms as do other infections the most prominent being pain frequency of urination, and hematuria The frequency is more prominent at night, dysuria may be quite distressing, becoming even more severe when the bladder is ultimately involved Hematuria is usually mild but pus is always present There may be a dull pain in the loin occasionally there is actual renal colic Systemic symptoms may be absent or very mild unless the disease be far advanced Careful examination will frequently demonstrate a tuberculous focus in the lungs

Diagnosis depends finally upon the demonstration of tubercle bacilli in the urine Pyelography will usually reveal evidences of disease in the pelvis and urine collected by ureteral catheter will contain pus and have the low urea content of impaired renal function

Syphilis—Syphilitic infection of the kidney usually occurs during the secondary stages of the disease and in its clinical and pathological features resembles the "pure nephrotic state discussed above under Bright's disease Under present day conditions it is rare to see the massive edema albuminuria may be the outstanding feature that attracts attention to the condition If the patient has been receiving mercury the renal lesion might be ascribed to

toxic effects of this drug but mercury will never produce the metabolic changes seen in the nephrotic state

The *prognosis* is good as the condition usually clears under *treatment of the syphilis*

Treatment of Renal Infections.—Cortical abscess requires antibiotics or chemotherapy if signs of perinephric abscess develop surgical drainage is indicated No local treatment is useful for the multiple abscesses of septicemia but all measures should be directed to the treatment of the general condition

The discovery of the sulfonamides and the various antibiotics has made the successful treatment of pyelitis much easier and shorter in duration In many cases the exhibition of 1 gram (15 grains) of a sulfonamide (such as sulfadiazine) three times daily will be sufficient to bring the condition under control in a few days If the infecting organism be one of those that are susceptible to penicillin the intramuscular injection of this drug in dosage sufficient to keep up a good concentration in the urine will likewise have a rapid effect The majority of the organisms associated with this condition are gram negative and not susceptible to penicillin but good results can be obtained by using streptomycin in divided doses of 1 to 2 grams daily intramuscularly (see Chapter XXI)

The main principle in the treatment of pyelitis is to establish drainage which is best achieved by posturing the patient in such a position as will aid in relieving kinks in the ureter in general this implies lying flat on the back without head pillows but a small roll inserted under the lumbar curvature In some cases as in pyelitis of pregnancy it may be necessary to raise the foot of the bed to relieve the pressure of the uterus on the ureter At the same time flushing out from above should be promoted by the forcing of fluids Where there is no vomiting the total intake by mouth should reach a maximum of three to five liters daily for an adult as water may prove unpalatable fruit juices and "imperial drink" may be used freely If vomiting interferes with the fluid intake it may be necessary to administer fluids by rectum intravenously and subcutaneously

Mandelic acid can be given in the form of ammonium mandelate of which approximately gr. xxxv (2.3 Gm.) should be given by mouth four times daily It is essential that the pH of the urine should be kept below 5.3 if it be higher than this it will be necessary to administer ammonium chloride as well in sufficient dosage to produce the desired degree of urinary acidity

In certain cases cystoscopy with catheterization of the ureters may be necessary to relieve obstruction and overcome stasis Occasionally the renal pelvis is washed out with dilute antiseptic solutions

The *treatment of tuberculosis of the kidney* in the majority of cases is surgical involving excision of the affected organ If the disease is bilateral or if there be extensive disease elsewhere, treatment may have to be symptomatic only

Syphilis of the kidney usually responds well to treatment which is preferably with bismuth at the beginning followed by arsenicals and mercury later

In this condition the apparently paradoxical situation arises of using the metals which may injure the kidney to treat a condition characterized by massive albuminuria Penicillin has overcome this impasse

Nephrolithiasis

(Renal Calculus)

In this condition solid foreign bodies known as "stones" are found in the calyces or pelvis of the kidney, which may give rise to symptoms, or be relatively asymptomatic

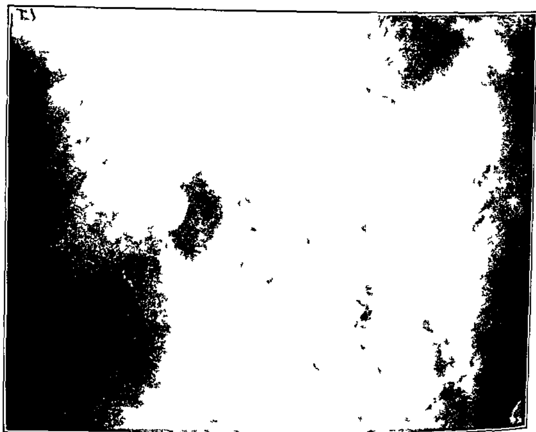


Fig 461 —X ray showing a single calculus in the pelvis of the right kidney

The chief factors in the formation of renal calculi are perversions of metabolic processes infection and stasis in the urinary tract Various theories have been advanced to explain the mechanism of stone formation one school holding that there is a central nucleus of colloids (often of infective origin) on which the crystalloids are precipitated the other that the crystalloids are deposited from the urine in which they are present in concentrated solution In the latter case precipitation follows the physical laws of solution, in which salt and hydrogen ion concentration are important factors In all cases stasis and a concentrated urine appear to be the chief physiological factors while infection may play a further part in the process Vitamin A deficiency (see page 784) has also been accused of being responsible for nephrolithiasis through

the resultant keratinization of the epithelial lining of the renal pelvis and the ureter Sulfonamides are today a relatively frequent cause

In general calculi may be classified according to their chemical composition the principal types including calcium uric acid, phosphate, oxalate and rarely cystin Recent studies have served to emphasize that calcium stones may be the outstanding indication of hyperparathyroidism, in which the urinary excretion of calcium is greatly increased, in these cases estimation of the level of calcium and phosphorus in the serum may be of great importance in determining the etiology Similarly in the individual with a gouty diathesis study of the uric acid in blood and urine may yield significant evidence



Fig 46 —X ray showing staghorn calculus in the pelvis of the left kidney

Phosphate stones are more usual in cases with stasis and infection oxalate stones are usually combined with calcium to form the relatively insoluble calcium oxalate Stones several generations ago were usually found in children (vitamin A deficiency?) while now they may appear at any age period but are more common in the third and fourth decades and in men than in women

Symptoms—The best known and most easily recognized symptom is renal colic A typical attack begins with severe pain in the loin or back radiating around to the front of the abdomen and down to the external genitalia or the inner side of the thigh The radiation corresponds to the region involved loin pain from the renal pelvis abdominal and genital from the ureter according to the level The pain is extremely acute colicky in nature and is usually

associated with varying degrees of shock, which may produce cold sweat, vomiting and general collapse Frequent and painful urination is a prominent symptom caused by reflexes from irritation of the pelvis and ureter The urine contains blood in gross or microscopic amounts, a few pus cells may also be present Generally the old rule holds true, "the smaller the stone the greater the colic" a "crystal" may cause severe colic and yet be too small to cast a recognizable x ray shadow This type is frequently spoken of popularly as "gravel" The colic usually lasts until the stone passes down into the bladder or slips back into the pelvis, when the relief is great, and the exhausted patient usually sinks into sleep



Fig 463 —X ray showing a small calculus in the left ureter

Where stasis is marked and infection is present symptoms may be vague or consist merely of pain in the back or "lumbago" In these cases large calculi may be deposited in the pelvis and calyces forming the typical stag horn calculus Frequently symptoms may be absent and the calculi are found by x ray in the course of investigation of the renal tract or vertebrae

The sequelae of calculi depend upon the anatomicophysiological changes produced as a rule small calculi cause no lasting ill effects, and are usually passed in the urine Larger stones may become impacted in the ureter when they may ulcerate through or more commonly give rise to atrophy of the kidney or hydronephrosis as discussed below In the rare instance where there is bilateral impaction of stones, anuria will result, with death if the con

dition is not relieved In these cases there is rapidly increasing nitrogen retention in the blood, but no changes in the ocular fundi, nor is there necessarily hypertension Uremic symptoms may not occur or they may appear only as a terminal event

Diagnosis—Where there is a typical colic and hematuria, the diagnosis is easy As stated above x ray examination may give negative results in the presence of a small stone In less typical cases ultimate diagnosis may rest upon x ray and cystoscopic examination In some instances the x ray shadow of a phlebolith has appeared to be typical of a calculus until cystoscopy and ureteral catheterization showed that the shadow did not correspond with the position of the ureter

Acute appendicitis and gallstone colic may occasionally offer difficulties in the differential diagnosis of a right renal calculus

Treatment—Acute colic will require large doses of sedatives As a rule a quarter grain of morphia by hypodermic injection will be quite ineffectual in the average adult, it is better to give a half grain at once and repeat sixth or quarter grains according to the indications If the pain refuses to yield it may be necessary to give whiffs of chloroform though it should be borne in mind that this measure is not without danger After the pain has been relieved the patient should be kept warm and allowed rest Fluids should be forced to "flush out" the urinary tract by increased secretion Frequently morphia will relieve the spasm of the ureter sufficiently to allow the calculus to pass to the bladder and so out the urethra Frequently the stone can be recovered when passed, though if it be small it may be missed unless all the urine be strained through cheesecloth when the calculus is left visible In more chronic cases treatment becomes a surgical problem

Following the passage of a stone there may be formation of others In some cases this can be prevented by increasing the fluid intake with the purpose of keeping the urine dilute If there be a gouty diathesis appropriate treatment for this condition should be instituted in cases due to hyperparathyroidism surgical removal of the hyperfunctioning glandular tissue is indicated

Hydronephrosis

Hydronephrosis is the term applied to that condition in which there is dilatation of the renal pelvis with pressure on and subsequent atrophy of the renal parenchyma It is induced by any condition which interferes with drainage of the urine once it has been secreted by the kidney such as stricture of the urethra prostatic hypertrophy impacted ureteral calculus kinking of the ureter external pressure on the ureter as from neoplasms etc Where obstruction is complete there is usually a small degree of dilatation of the tract above the site of obstruction followed rapidly by atrophy of disuse of the renal tissue it is in incomplete obstruction such as the intermittent type that dilatation proceeds to the greatest extent Sooner or later infection enters the stagnant urine and inflammatory changes take place Ultimately only a shell of kidney substance is left in which there is little or no function

enclosing a collection of infected urine or pus This final condition is differentiated as *"pyonephrosis"*

In the early stages the symptoms are those referable to dilatation and stretching of the pelvis and capsule, later those of the septic state, and of failing renal function become more prominent Thus there is dull aching pain in the loin or abdomen, frequency, pyuria, fever and a general septic state as the condition progresses Cystoscopy with pyelography and estimation of the renal function by dye excretion and urea content of the urine collected by ureteral catheter will furnish evidence of the degree of involvement.

"Dietl's crises" are acute intermittent occlusions of the renal pedicle due to torsion when the poles of a freely movable and displaced kidney assume an anteroposterior position There is acute pain in the loin, chills, pyrexia, sweating, leucocytosis, *and often collapse There is also some hematuria* and oliguria, although there is frequency of desire A tumor is palpable in the loin which usually disappears on manipulation by returning the kidney to its normal position

Prognosis depends on the degree of interference with drainage, and the possibility of restoring free drainage by relieving the cause of obstruction Treatment is thus usually surgical in nature, and may involve nephrectomy

TUMORS OF THE KIDNEY

Clinically these fall into two main groups, those of childhood occurring from birth to about five years, and those of later life from forty years on These groups correspond in general pathologically with the embryomata and sarcomata, and the carcinomata (including the hypernephromata) respectively In generalized carcinomatosis, metastases may appear in the kidney often bilaterally, the primary tumors, however, are practically always unilateral Benign tumors of the kidney are not frequent and are rarely diagnosed clinically

Of the signs and symptoms the earliest and most important is hematuria which is usually spontaneous and may be quite profuse, often there are repeated attacks It is painless unless clots be formed which in their passage to the bladder may give rise to ureteral colic Pus is not usually found in the urine

The tumor mass may not be palpable early in the disease process, but later it can be felt in the loin or through the abdominal wall, it usually moves with respiration

A sign which has been stressed is the presence of a varicocele which does not disappear when the patient lies down due to pressure of the tumor mass on the spermatic vein of that side Pain in the loin may be present as a dull ache, it is ascribed to stretching of the kidney capsule Renal function is usually relatively little impaired throughout the course and death takes place from the cachexia associated with malignant growths Metastases in the lungs are not infrequent

Diagnosis —In the early stages the hematuria may *be suggestive* of renal calculus or tuberculosis, in the later stages the mass may be confused with

congenital cystic kidney or pyonephrosis Cystoscopic examination and pyelography with x ray may be of aid in making a differential diagnosis

Treatment—Treatment is surgical, in some cases it may be possible to remove the growth completely, but usually this is impossible when treatment will be purely palliative

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CHAPTER XIX

INFECTIOUS DISEASES

In the preceding chapters some infectious diseases have been described because of the fact that their principal clinical manifestations warranted their being considered as diseases under a special system rather than under their etiological cause, which is the customary method. This latter does not seem to have any particular virtue as it dissociates the infection from the clinical picture of its first manifestations which is the important period for its recognition if specific treatment is to be most efficacious.

The diseases now to be considered, arranged according to their etiology, are the following:

Bacillary	*Spirochetal*	*Virus Diseases*
Leprosy	Syphilis	Smallpox
Tetanus	Yaws	Varicella
Tularemia	Rat bite fever	Herpes zoster
Anthrax	Relapsing fever	Rabies
Glanders		Dengue
Plague	*Coccal*	Epidemic pleurodynia
	Staphylococcal septicemia	Pappataci
Rickettsial	Streptococcal septicemia	Lymphogranuloma inguinale
Typhus fever	Erysipelas	Foot and mouth disease
Tsutsugamushi disease	Gonorrhea	Swineherd's disease
Rocky Mountain fever		
Trench fever	*Protozoal*	*Nematode*
Carrion's disease	Leishmaniasis	Filariasis
Q fever	Trypanosomiasis	
Bullis fever	Malaria	
Rickettsialpox	Toxoplasmosis	

But this classification does not give information as to the manner in which the patient is infected. Furthermore it is important to appreciate that certain diseases may be recognized by a characteristic primary lesion at the portal of entry of the infecting agent, and an early diagnosis can thereby be made. In others it may not be particularly specific or may be so minute as to pass unnoticed by the patient or the physician. The agent when inoculated may enter the blood stream directly and so be disseminated. Again it may pass along the lymphatic channels and be temporarily or permanently arrested by the regional lymph glands or first line defense from where it may eventually be disseminated via the blood stream to all the tissues. These may not all be equally affected and the secondary lesions may vary considerably in different tissues. This is probably determined by their power of defense or lack of defense. Occasionally the virus travels along special tissues as the nerves in rabies, and as a consequence the entire localization in this disease is within the nervous system. The majority of these diseases gain access through the skin either on account of abrasions, punctured wounds or bites of various animals or insects. In some diseases the means of transmission and inoculation often shed light upon the possible diagnosis. There is an important group that is inoculated directly through the skin or mucous membrane and the place where this occurs

can be fairly definitely located in most instances There is not necessarily any detectable break in the continuity of the skin but a minute injury undoubtedly is present to allow of the entrance of the infection In some the mucous membrane undoubtedly offers an excellent medium for the growth of the virus, and as it sinks deep into the interstices of this surface, it produces local irritation and reaction which open the way for its deeper penetration Immediate irrigation of the part will frequently prevent these local lesions and therefore presumably the surface tissues have not been penetrated at the time of contact, or if so, very superficially, and the virus may be killed or removed before it has a chance to become entrenched in the deeper tissues There is another group in which the infectious agents are carried to and deposited on the surface of the skin by lice, ticks and fleas Either through the bites of these insects or through scratching caused by the local irritation, the virus gains entrance through these superficial abrasions In still another group the infection is directly inoculated into the blood stream by blood sucking insects such as mosquitoes and sand flies Finally there is a small group of cases in which the portal of entry cannot be explained by any of these means All of these diseases may be grouped as shown in Table XVIII

TABLE XVIII

Skin Abrasions or via a Mucous Membrane

Staphylococcal septicemia
Streptococcal septicemia
Erysipelas
Syphilis
Yaws
Lymphogranuloma inguinale
Gonorrhea
Tularemia
Anthrax
Glanders
Tetanus
Foot and mouth disease

Animal Bites

Rabies
Rat bite fever

Lice Ticks and Fleas

Typhus fever
Tsutsugamushi disease
Trench fever
Rocky Mountain fever
Relapsing fever
Plague
Swineherd s disease
Q fever
Bullis fever
Colorado tick fever
Rickettsialpox

Blood Sucking Insects

Malarial fever
Yellow fever (see page 36)
Filariasis
Dengue
Pappataci
Leishmaniasis
  Kala azar
  Oriental sore
  Espundia
Carrion s disease
Trypanosomiasis
  African sleeping sickness
  Chagas disease

Unclassified

Smallpox
Varicella
Herpes zoster
Lymphocytic choriomeningitis
Leprosy
Infectious mononucleosis
Epidemic pleurodynia
Toxoplasmosis
Erythematoses
Lupus erythematosus

SEPTICEMIA

Definition —An exact definition of septicemia is difficult as it is a clinical symptom complex or syndrome which may be due to many different bacteria. There are certain closely related terms applied to different phases or states resulting from bacterial causes of disease that it might be well first to be clear about

Toxemia should be reserved for those conditions where an endotoxin or an exotoxin produces symptoms but the bacteria do not invade the blood stream or specific tissues, but the toxins do, as diphtheria toxemia and tetanus toxemia

Pyemia should be applied where abscesses or purulent collections occur in the *fixed tissues If these are scattered and* cannot be accounted for by lymphatic spread the organisms must have been carried by the blood stream but this may not be capable of bacteriological proof nor may there be any evidence to indicate that the bacteria grow in the blood or within the blood vessels

Septicemia is a state in which organisms are in the blood on occasion but even if not demonstrable by bacteriological methods they are suspected of being disseminated The principal feature however is a severe general toxic reaction often characterized by chills and even rigors This category does *not necessarily include the group of specific infections mentioned elsewhere* although severe toxic symptoms may also be present The most outstanding examples are found in instances where the blood vessels (veins) are the source of a blood stream infection

Bacteriemia should be strictly applied to those states where bacteria are recovered from the blood stream There may be either a pyemia or a septicemia present On the other hand there may be comparatively little or no evidence of either

There are a number of specific diseases in which the organisms can be *grown from (or seen in) the blood either during the early stages of the infection,* or *periodically during its course, such as typhoid fever, pneumonia,* meningococcal meningitis anthrax glanders undulant fever, relapsing fever, subacute bacterial endocarditis (lenta), etc These can all be classed as septicemias and some as pyemias as well, but on the other hand they are also clinically specific infectious diseases If the organisms were found in the blood stream and there were not the specific clinical manifestations of the disease, then they would properly be called bacteriemias

Etiology—*General*—Man is being constantly exposed to invasion by bacteria and there is little doubt that fleeting bacteriemias occur without causing any clinically recognizable symptoms On the other hand for no accountable reason they may be assailed by organisms which they have been harboring on their skin and mucous membranes as harmless parasites There are however certain contributing factors which may play a role in this warfare These infections are more common in the old and the young, in cold weather rather than in the summer in the late winter rather than in the autumn, in chronic alcoholics in such diseases as diabetes mellitus cardiorenal disease arteriosclerosis cirrhosis of the liver, cancer where there has been undernutrition exhausting labor or great mental anxiety or worry They are more common in women on account of puerperal sepsis The blood and associated protective cells undoubtedly can usually cope with a mild bacterial invasion but why they cannot do so always is not wholly known as our knowledge of acquired and natural immunity against infection is still incomplete It is known that the blood possesses certain bactericidal powers and also affords some important aid to the leucocytes and to the fixed cells in the reticulo endothelial system of the spleen

liver, bone marrow and lymph glands to carry on their work of phagocytosis and destruction of bacteria Apparently at these periods of susceptibility there is not only a reduction in the protective properties of the blood, but also through some unknown effect the cells cannot properly fulfill their duty It may be due to their debility, intoxication, fatigue, lack of response to stimulation or something else—we do not know, and leaves room for much speculation It is known, however, that in many of these cases the humoral protective bodies of the leucocytes are in abnormally small amounts or totally absent

Specific—The bacteria which produce a septicemia are numerous, and it is not our purpose to discuss them all in detail The more important are the following hemolytic streptococci, nonhemolytic streptococci pneumococci, staphylococci meningococci gonococci, *B coli B pyocyaneus, B mucosus capsulatus B influenzae B proteus, B faecalis alcaligenes* etc Of these the first seven are the most important Some of them have been considered under acute and subacute endocarditis where the principal lesion may be situated or where it is but an incidental finding

Symptoms and Signs—It is not the present purpose to deal with all forms of septicemia There are two however of great importance which require special mention namely the streptococcus and staphylococcus The general clinical characters of the other nonspecific organisms are similar to these The incubation period varies considerably but as a rule does not exceed a few days except when the septicemia follows upon a chronic infection when it is totally unknown The portals of entry are similar for both with occasional emphasis on a certain route for one or other of them

1 Skin wounds—varying from a scratch to large denuded areas (staphylococcus)
2 Puerperal uterine infections (streptococcus)
3 Paronychia boils carbuncles bed sores and burns (staphylococcus)
4 Otitis media mastoiditis lateral sinus thrombosis (streptococcus)
5 Ethmoiditis and sphenoiditis (streptococcus)
6 Tonsillar infections particularly scarlet fever and septic sore throat (streptococcus)
7 Alveolar abscesses (streptococcus)

When a septicemia occurs in the course of empyema osteomyelitis pyelitis etc., these might be designated as portals of entry but they are not strictly so as the septicemia is but a feature of the infection However this might also be held with equal reason for most of those mentioned above if we are to be strictly logical It may now be asked why a septicemia should arise from such slight causes as some of those mentioned The answer is quite obvious in some In puerperal sepsis there are infected thromboses in the uterine veins also there is an intravascular infection in lateral sinus thrombosis If this is not present or there is no infected thrombus in some of the veins draining the infected mastoid or ear the septicemia will cease as soon as these latter are cleared out, and similarly in ethmoiditis and sphenoiditis In fact in most cases of septicemia a local infected thrombosis will be found at the portal of entry It may be extremely small and the wound may be healed without its presence

being suspected It is doubtful whether a septicemia will continue if this is not the case In other words bacteria seldom persist in the blood stream unless renewed from some such source or from a focus on the endocardium as in bacterial endocarditis This is particularly the case in small skin wounds

The most important clinical feature of these *infections is pyrexia This* is usually of the septic type that is intermittent However this is not at all constant and there may be periods of apyrexia Chills and rigors are common and may occur with such regularity as to suggest malaria There are frequent sweats and great thirst The heart rate is rapid and the respirations may be slightly accelerated in proportion to the pyrexia but this is not conspicuous unless pneumonia develops when typical tachypnea appears There is a leucocytosis due to increase of granulocytes and the spleen is enlarged and usually palpable There are the other usual signs of infection headache malaise, general pains, and exhaustion A rapid anemia is common Erythemas are frequent in septicemia as is also purpura These have already been described in both infections under bacterial endocarditis (see Chapter VII) Metastatic abscesses are not common with the streptococcus but are with the staphylococcus These may occur in any tissues but especially in the lungs, spleen and kidneys In both a metastatic pneumonitis is common Jaundice is frequent as is hematuria A true nephritis is more common with the streptococcus and pyonephritis with the staphylococcus

Course—The course varies greatly In staphylococcus septicemia *in children* death may occur within forty eight hours Such cases are classed as fulminating and occur in other infections before specific signs appear as in epidemics of influenza meningitis scarlet fever septic sore throat etc The majority of cases last longer and may be classed as the acute type while a small number may continue for weeks and even months and are called chronic The duration is determined by the virulence of the organism and the resistance of the host The disease usually terminates by exhaustion with coma and the other signs of intense intoxication Local abscesses in the brain lungs liver or kidneys may modify the course

Diagnosis—The presence of a general infection is usually readily recognized and the majority soon exhibit the special features which lead to their identification as a specific disease In others this may be delayed for some time as in typhoid and undulant fever Although a septicemia may be suspected and even a shrewd guess made as to the particular organism causing it the correct diagnosis can only be proved by the bacteriological examination of the blood This should not rest on one examination only but if negative the first time it should be repeated In such cases cooperation and consultation between the clinician and bacteriologist are imperative if satisfactory results are to be obtained All the facts should be given to the latter who should see the case frequently with the clinician All bacteria do not grow equally well on the same media and some require quite a specific environment This is within the knowledge of the bacteriologist who must be governed by the probabilities indicated Urine cultures *may also be helpful*

Prognosis—This has been to some extent indicated under the course of the disease All cases are by no means fatal especially streptococcal septi

cemia Although it is the more common and more deaths occur from it, there are also many more recoveries, in fact it is likely that many recover without being recognized True staphylococcal septicemia is relatively uncommon but up to the last few years the mortality was almost 100 per cent There is no doubt again that some of these are not recognized and may recover, especially the more chronic cases in whom multiple abscesses form These may continue to appear with intermittently positive blood cultures In such it is certain that all foci have not been detected These are usually metastatic The outcome is also governed by prompt, energetic and rational treatment which primarily depends upon early bacteriological diagnosis

Treatment—To recount all of the measures which have been advocated for the treatment of septicemia would not only be impossible but worse than useless It is obvious that the usual general measures used in the treatment of any general infection should be employed, particularly rest, a diet of sufficient calories, and abundant fluids by mouth, and intravenously or per rectum if necessary Pyrexia and nervous symptoms should be controlled by hydrotherapy *Surgical measures* are indicated to effect free drainage of all approachable purulent collections as in mastoiditis, otitis media, sphenoiditis, ethmoiditis, empyemia, osteomyelitis, suppurating wounds cellulitis, carbuncles, etc If the portal of entry is in the skin and is of small area as in some cases of staphylococcal septicemia in children, it should be excised rather than incised, so removing the whole of the infected area including the small veins immediately draining it A small thrombophlebitis one cm long may be the cause of a fatal infection Healthy tissue should not otherwise be invaded by surgical methods Trauma to the surrounding tissues should be avoided at all costs The local reaction about the suppurating area should be left intact as it is an attempt to localize the infection but the necrotic and suppurating contents should be removed by all means at our command and localized pockets opened for free drainage Heat should be applied in the form of hot saline or hypertonic packs and frequently renewed so as to promote a free serous discharge All sinuses should be kept open and draining freely *The* chemotherapeutic and antibiotic treatment of septicemias depend upon the specific organism causing the disease As stated in preceding pages these methods of therapy will be dealt with in a separate chapter (see Chapter XX)

ERYSIPELAS

Synonym—St Anthony s fire

Definition—Erysipelas is a specific disease of the skin caused by the hemolytic streptococcus and is characterized by a spreading erythematous edema with a clear cut margin

Etiology—Erysipelas is not as common today as in years gone by when it was much dreaded particularly in surgical practice when epidemics especially in hospitals were frequent It is not caused as was one time thought by a specific strain of streptococcus but may be due to any one of several types of Group A streptococcus It was at one time thought that strains of the organism which caused erysipelas produced a specific toxin for this dis

ease This concept has now been discarded It is more common in women than in men, and during the middle decades Acute illnesses, operation, chronic diseases and alcoholism predispose to its occurrence in fact those conditions which seem to render *septicemia more liable are also influential in* the present instance

Symptoms and Signs—The incubation period as in all streptococcal infections is about three days The portal of entry is through a skin wound although this may be such a small break in its continuity as to be invisible On the other hand it commonly developed about a surgical wound This is rare today *The onset is sudden but not usually explosive* with a chill and rigors There is malaise, headache anorexia and pyrexia This last may be high without definite character, as it is either continuous or remittent, but never intermittent



Fig 464—Erysipelas of the face showing characteristic edema (*From* Sutton and Sutton Diseases of the Skin)

The most frequent site is the face particularly on the nose from which it spreads over the cheeks in a butterfly like distribution It may, however, occur on any part of the skin as about the umbilicus in the newborn the vulva in the puerperium around chronic ulcers, operation wounds or in the nasal and nasopharyngeal mucous membrane in association with sinus and tonsillar infections

The appearance of the lesion is quite characteristic wherever it occurs The skin is bright red and there is a swollen or edematous clear cut slightly elevated margin which slowly creeps into the surrounding tissues while the older areas show definite improvement The *periphery may be indented from* fingerlike protrusions which represent the irregular progress of the infection along the skin lymphatics There may be multiple sites of infection either proximal when they may unite to form a more irregular lesion or on distant areas such as the face and the leg or the vulva and other areas which have no relation to each other except as being simultaneous portals of

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All attempts at specific therapy with sera have now been superseded by sulfonamides and penicillin particularly sulfadiazine which usually controls the infections in 36 to 48 hours (see Chapter XX)

SYPHILIS

Synonym—Lues venerea

Definition—This is an acute and chronic disease due to a specific organism of the spirochete species called the *Treponema pallidum* It is a disease which probably has been existent for many centuries, but it occurred in epidemic form in the sixteenth century, closely following the return of Columbus from his voyages to the West Indies

Etiology—It is difficult to obtain accurate figures as to its incidence in the population of North America at the present time *It is noted that it is* more common among the Negroes than among the whites Such statistics as are available would indicate that the incidence varies from 5 to 25 per cent in an ordinary hospital population Perhaps on the whole 10 per cent would be a fairly accurate estimate

The *Treponema pallidum* is a delicate spiral with from six to ten turns, and its total length is about 10 microns The spirals are regular and the movement of the organism is a rotating one around its long axis It is extremely labile and is killed by simple soap and water drying and exposure to even the weakest disinfectants It has not as yet been grown on artificial medium but can be transmitted from animal to animal by direct inoculation It is found in large numbers in the tissue juices of the local lesions It is not stained readily but is best demonstrated by Giemsa s solution or the Fontana silver method A simple manner of demonstrating them is by making a mixture of a little of the tissue juice with Gunther s India ink on a glass slide and allowing it to dry Under the oil immersion the Treponema will be seen as fine white spirals on a black background They are most readily detected in the tissue juice when examined with dark field illumination

The spirochete is transmitted from man to man by direct contact although occasionally it has been reported as being conveyed by musical instruments drinking cups hypodermic needles, blood transfusions etc The inoculation may occur on any cutaneous or exposed mucous surface The most frequent manner of inoculation is during sexual intercourse and as will be seen later the portal of entry is more easily recognized in the male than in the female Another important and common means of transmission is by kissing or through human bites Doctors and nurses are sometimes inoculated on the hands through contamination with syphilitic exudate This was more common before rubber gloves were so much in vogue Suckling infants have been known to be infected through a syphilitic lesion upon the nipple of a wet nurse Although the venereal contact is the most common method of inoculation there are areas in the world where this disease is supposed to be endemic and practically the whole of the population is infected in childhood In these places it is not a venereal but an ordinary contagious disease This is particularly true in certain parts of Arabia where 90 per cent of the population

infection The mucous membranes are sometimes involved but much less frequently than the skin Although it spreads from the mucous membranes to the skin, the reverse is exceedingly rare The larynx is rarely involved, but if so, usually causes death from suffocation When it spreads from the vulva to the vagina and endometrium a fatal septicemia is the rule Bullae and vesicles *often develop over the more acute* portions of the skin lesion, and sometimes local suppuration due to secondary infections or extensions to the subcutaneous tissues occur while gangrene is rare The neighboring lymph nodes are usually enlarged but rarely suppurate Extension to adjacent tissues such as the orbit and from thence to the meninges and cavernous sinus, or into the paranasal sinuses occasionally happens

The constitutional symptoms may be extreme with great prostration and delirium particularly at night There is a leucocytosis and the spleen is enlarged but seldom palpable The urine contains a trace of albumin and a few casts while nephritis occasionally occurs (one per cent)

A bacteriemia is unusual but when it does occur, metastatic lesions such as endocarditis arthritis pericarditis, pneumonia, pleurisy and phlebitis may develop

Pathological Anatomy —The streptococci are found in the lymphatics of the skin along the advancing margin, but are absent in the other parts of the lesion Surrounding the lymph channels there is an intense infiltration with mononuclear cells Visceral changes such as cloudy swelling common to all infections are found but when there is a bacteriemia, local lesions also may develop

Diagnosis —This is usually done by inspection, but it must be differentiated from a simple local erythema which, however does not have a raised margin Acute eczema or dermatitis may suggest erysipelas, but there is no pyrexia or systemic symptoms Cutaneous phlegmon may be more difficult to exclude but there is usually a much deeper inflammation with brawny induration and not the clear cut edematous margin found in erysipelas

Course and Prognosis —The duration of the disease is indefinite It may creep over large areas and indeed may eventually cover the greater part of the body As it spreads the older areas subside Relapses and recurrences are common and it may recur year after year at the same time and the same place or may be associated with some periodic occurrence such as menstruation When an area of skin is frequently involved there may develop permanent blockage of the lymphatics leading to a local elephantiatic condition Usually the disease lasts but a few weeks and complete recovery results The mortality varies being reported by different authorities as from 5 to 10 per cent The age and previous condition of the patient greatly modify this In previously healthy adults it is less than 1 per cent, but when blood cultures are positive it is close to 100 per cent

Treatment —The general treatment of this disease follows the same principles as for other infections namely bed rest high caloric and protein diet large amounts of fluids The pyrexia and nervous symptoms should be controlled by hydrotherapy The local lesion should be kept clean and the pain relieved by hot or cold applications

Primary Symptoms and Signs—The incubation period is from ten to sixty days, usually about twenty one days During this period there are few or no symptoms The chancre may develop on many extragenital sites such as the finger the tongue the lip, the tonsil the mons veneris lower abdomen eyelid, nipple, etc It is usually single although occasionally two chancres may be found particularly on contiguous mucous membranes It is painless and without irritation It heals slowly when untreated, leaving a pigmented scar which may be visible for many months, but this in time completely disappears or may leave a smooth whitish surface Recurrent chancre or *chancre redux* results from Treponema remaining viable in the scar There are seldom any general symptoms during the early period of the chancre, but with the invasion of the blood and dissemination of the spirochete, symptoms of a generalized *infection such as malaise, chilliness pyrexia, may be more or less prominent* incident with its massive destruction In addition to the local lymphatic enlargement a general adenopathy occurs There is also some anemia which



Fig 46 —Chancre of the penis with widespread edema. (From Sutton and Sutton Diseases of the Skin)

may be extreme Generalized pains in the bones and joints may be a prominent feature In many cases these symptoms are entirely absent, while in others they may assume a virulent character giving all the evidences of a severe general infection The spleen may be palpable with icterus and enlargement of the liver The interval between the appearance of the chancre and the development of these general symptoms is called the secondary incubation period It may vary considerably in duration

Secondary Symptoms and Signs—With its termination and the appearance of the general toxic reaction acute lesions in many organs may develop such as iritis meningitis valvulitis and diffuse and variegated skin eruptions The latter at one time attracted considerable attention and made syphilis practically a dermatological disease At that time the general nature of the infection was not appreciated as it has been since the demonstration of its definitely infectious and systemic character There is hardly a dermatological manifestation which cannot be simulated by syphilis There are a few important points which should suggest the syphilitic nature of skin eruptions They are usually painless and not itchy They are apt to infiltrate centrifu

are syphilitic It is acquired in childhood, is nonvenereal and is called "bejel," and is distinguished by these people from *franghi* or the "foreign disease "

It may be transmitted from a syphilitic mother to the fetus This is known as congenital syphilis Treponema have been proved to be present in the semen of latent syphilitics, but whether such can infect the ovum without its also infecting the mother first is open to considerable question

At the point of inoculation there is probably a slight abrasion of the epithelium through which the Treponema penetrate They may pass from here to the general circulation without producing a local reaction recognizable by the patient, or it may be so insignificant as to be considered of no importance, and a patient may quite conscientiously state that he has never to his knowledge been so infected In women this must be particularly common as the primary lesion within the vagina or on the cervix uteri may pass unnoticed, and similarly extremely mild reactions occurring on the labia minora, and less frequently on the labia majora attract but little attention The characteristic primary lesion is a hard, sclerosing nodule which on account of its cartilaginous firmness is called a chancre, or hard sore, as distinguished from the chancroid or soft sore which although venereal, is not syphilitic It may remain as a small hard papule but usually the surface ulcerates, leaving a clear cut, crater like depression This ulceration may be serpiginous or even gangrenous (see Fig 465) They are indolent in healing unless treated

Pathological Anatomy—The primary lesion is quite characteristic There is infiltration with leucocytes lymphocytes and plasma cells in the perivascular tissues of the smallest blood and lymph vessels followed by an endovasculitis eventually affecting the intima and leading to obliteration of their lumen There is an overgrowth of connective tissue with spindle cells, epithelial cells and a few giant cells The lesion will be found to contain large numbers of Treponema which may invade the blood stream and be carried throughout the circulation Others enter the lymphatics and travel to the regional lymph glands most commonly to those in the inguinal area These may become enlarged and hard but eventually return to about their normal size without further local lesion In rare cases necrosis and suppuration occur, the gland softens and eventually discharges through the skin but gonorrhea and lymphopathia venereum must be excluded These are called buboes Probably before the chancre has fully developed the Treponema have passed beyond it and have either invaded the blood stream or the lymphatics This widespread distribution of the spirochete may lead to the so called " secondary" or disseminated lesions *which usually regress and in some the* " tertiary" or granulomatous lesions develop The anatomical changes of these will be discussed later In many individuals infected with syphilis neither primary, secondary or tertiary lesions can be found at autopsy indicating as in tuberculosis that a local lesion need not necessarily be a general one or at least that a general dissemination of the spirochete need not produce generalized lesions This would suggest that the Treponema may be destroyed in the tissues without causing any anatomical change

due to the dilatation of the capillaries which contain large numbers of Treponema and the tissue juice from such is highly contagious There is another macular eruption which may occur at the same time or somewhat later, which is more elevated and instead of being rose colored is a coppery brown These lesions result from more pronounced pericapillary and capillary infiltration, and persist longer and often leave a definitely pigmented area, or in the darker races areas lighter than the surrounding skin



Fig 468 —Grouped, or corymbose papulo squamous syphiloderm of six weeks duration (Courtesy of Dr J B Shelmire From Sutton and Sutton Diseases of the Skin)

The next eruptions are papular These vary in size from a pinhead to the size of a nickel They are definitely elevated and are due to a still more extensive productive lesion with considerable vascular and perivascular infiltration They appear not only on the torso but on the scalp where they lead to a moth eaten alopecia on the palms of the hands and the soles of the feet where there is a tendency for them to become dry and cracked which may lead to ulceration They may also occur in the nails producing syphilitic onychia and paronychia All these lesions contain large numbers of *Treponema but if they do not ulcerate* or macerate are not as infectious as are the macular and roseolar lesions They occur however in considerable num

gally and disappear centrally, thus giving a roughly ringlike appearance to some and an umbilicated appearance to others The first eruption is usually of a macular or roseolar character which is highly infectious in moist areas (mucous patches) It is distributed mostly over the chest and abdomen It may vary in intensity from a diffuse blush to definite rosy macules It is



Fig 466 —Maculopapular syphiloderm of trunk (From Sutton and Sutton Diseases of the Skin)

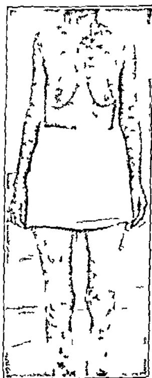


Fig 467 —Papulopustular syphiloderm ata in a neglected case of lues (Courtesy of Dr Ott Leslie Castle From Sutton and Sutton Diseases of the Skin)

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bers around the genitals and anus where on account of the local moisture maceration occurs These are called condylomata and are extremely infectious, as are similar lesions upon the mucous membranes of the lip, buccal cavity, and tongue These are called mucous patches The presence of these lesions and of a primary chancre about the mouth account for the frequent inoculation of noninfected individuals by kissing This papular eruption may become infected and form pustules, and is then called a "pustular syphilide" They may resemble acne, impetigo, variola, or may involve the skin in extensive suppuration An eruption of still later development is a nodular or



Fig 469—Condylomata of vulva and perineum (Courtesy of Drs Fordyce and Mackee From Sutton and Sutton Diseases of the Skin)

tubercular syphilide It is an elevated nodule with a cyanotic reddish color, and has the common attribute of the majority of syphilides in appearing in circles with a serpiginous progression When they heal they leave a distinct depression due to destruction of tissue with a brownish appearance The tubercles may be so numerous as to coalesce, involving large areas and they may ulcerate They are usually very persistent This tubercular eruption seems to occupy a position midway between the true secondary lesions in which there is not a pronounced cellular reaction and destruction, and the last or tertiary syphilitic lesion called the "gumma" These are more deep seated lesions appearing in the skin mucous membrane and viscera which ulcerate and lead to large areas of central necrosis They are extremely indolent and destructive when untreated

Tertiary Symptoms and Signs —So far the superficial lesions of syphilis only have been described It will be noted that there is a gradation between the early macular or roseolar lesions and the more deep seated and destructive gummata These however are but a few of the descriptive terms that may be applied to syphilitic dermatological lesions The other terms give a faint idea of the varieties of eruption that may be encountered, such as papulosquamosa of the palm of the hand, papulopustulosa papuloorbicularis, circinata miliopapulosa or lichenoids the leucodermata which appear so characteristically on the back and sides of the neck and may lead to a correct diagnosis on sight, the maligna or rupia frambesiformis, corymbiformis, tuberoserpiginosa, ulceroserpiginosa, diffuse lingual gumma In addition to the skin the mucous membrane of the mouth, pharynx nose tonsils, and larynx may be involved in similar lesions



FIG 4 0—Squamous syphilide of palm. (From Sutton and Sutton Diseases of the Skin)

As the *Treponema pallidum* is distributed to all tissues where there are capillaries syphilitic lesions may there develop Therefore it is an exhaustive procedure to describe them all in detail They have already been dealt with under lesions of the heart and blood vessels the esophagus, stomach, intestines, liver and organs of the genitourinary tract the nervous system etc It would serve no useful purpose to recapitulate these here It may be stated as an axiom that syphilis should be considered the possible cause of every chronic lesion or group of symptoms until proved to the contrary There are a few however which should be emphasized

Headache and pains in the bones which are particularly severe at night should be suspected as being syphilitic The lesion may be in the form of

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communicate between the tables of the cranium Syphilitic arthritis closely resembles tuberculosis and may be a true syphilitic lesion of the joints differing from the trophic destruction commonly known as Charcot s joint which occurs in locomotor ataxia and syringomyelia

All of these syphilitic lesions no matter where they may appear, are due to the localized syphilitic reaction about the small blood vessels It is true that some tissues are more often involved than others particularly the



Fig 4 —Syphilis bullosa (P 1 ff and M m ro ski From Sutton and Sutton Diseases of the Skin)



Fig 4 3—Depigment t or follo ing syphilit c ulcerati n of the skin in a Negro (From Sutton and Sutton Diseases of the Skin)

skin the aortic valves the aorta, the liver, the bones and the eye while in other tissues syphilitic lesions are comparatively rare There is however one system in which prominent and progressive lesions are common namely the nervous system In conformity with syphilis elsewhere the blood vessels of the meninges and parenchyma of the central nervous system may be involved and produce one or more of several clinical patterns These are not always

vascular obliteration, necrosis leading to osteitis, and osteomyelitis with discharging sinuses Periosteitis of the long bones, particularly of the tibia usually produces an extensive productive lesion causing the so called "sabre shin" It is at first an acute lesion with pain, swelling, tenderness, and redness These syphilitic bone lesions are among the few that produce pain Local exostoses may also occur Gummata sometimes produce extensive destruction of the bone and a spontaneous fracture may occur Small gummata

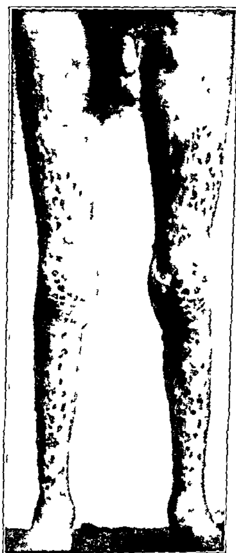


Fig 471—Rupial syphilid (Courtesy of Dr Otto Leslie Castle From Sutton and Sutton Diseases of the Skin)

usually pass unnoticed although they may leave an area of absorption recognizable by x ray A syphilitic spondylitis may produce stiffness of the spine and deformity Destructive lesions of the bones of the face and nose are also due to gummata and there may be a complete collapse of the nasal structure giving rise to a characteristic deformity (see Fig 1) There may also be perforation of the hard and soft palate Punched out syphilitic ulcers of the scalp or cranium are quite characteristic They are usually multiple and may

[illegible]

[illegible]

[illegible]

[illegible]

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clearly defined and there is often considerable overlapping of symptoms and signs They may indicate the presence of a local tumor caused by a gumma, a transverse myelitis, or an acute or chronic meningitis, while an arteritis leading to aneurysm or occlusion of a cerebral vessel may simulate the vascular accidents of arteriosclerosis, hypertension or a congenital aneurysm, and finally they may be degenerative as represented by general paresis and locomotor ataxia In order to avoid repetition and confusion, details of syphilitic diseases of the nervous system have been considered in Chapter XV



Fig 474 —Syphilitic alopecia showing typical moth eaten appearance of hairy scalp (Courtesy of Dr John A Fordyce and Dr George M MacKee From Sutton and Sutton Diseases of the Skin)

Congenital Syphilis

Syphilis is transmitted to the fetus from the mother and never directly from the father The mother is most likely to be infected within the first three years after the infection of the consort As each year passes thereafter this becomes less likely, but the mother may infect the fetus via the placenta for many years after her initial lesion The more recent the infection in the mother, the more likely is early infection of the fetus to occur If the fetus be infected early in the pregnancy it usually dies *in utero* and is expelled and there may be several such episodes before a living child is born On the other

hand, if the mother has been infected ten or more years before conception, miscarriages are not so frequent A child may be born at any time after the maternal infection exhibiting at birth unmistakable signs of syphilis, or it may be comparatively healthy but a positive Wassermann test will be found in both mother and offspring In syphilitic children where *the signs of infection* are not present at birth, these may appear at any time that is within a few months or years, or not until puberty or even later

In stillborn syphilitic fetuses, or in infants born with signs of syphilis, the Treponema are present in very large numbers in fact there is a spirochetemia They are particularly numerous in the liver adrenals lungs and the cutaneous lesions Such infants do not live more than a few days or weeks, and at autopsy there will be found *intense syphilitic lesions in the lungs liver* adrenals and to a less pronounced degree, in the kidneys and pancreas

Symptoms and Signs—These do not differ materially from those of the secondary stage in acquired syphilis There are however, certain features which are characteristic such as fissures about the angles of the mouth and in the mucous membranes of the cheeks There is a nasal discharge commonly called 'snuffles" The rashes are both macular and papular and sometimes bullous and are most *frequently found on the buttocks and the face* These have a coppery brown color Syphilitic erythema and eczema are also recognized The papules or more deeply seated lesions may coalesce particularly on the hands and feet and about the mouth, forming large confluent lesions Deep infiltration of these on the skin and mucous membranes of the lips may form an indurated mass which is called cheilitis diffusa " and when the fissures are deep and ulcerated they are called rhagades " The bullae *are the most serious cutaneous lesion and when the superficial covering is* removed leave large ulcerating areas There may be also alopecia and onychia as in adults

The less distinctive signs and symptoms are retardation of physical and mental development restlessness insomnia and the child may waken out of sleep with a high pitched cry or whine Enlargement of the liver is common and in the spirochetemic cases there is splenomegaly There may also be a pronounced *anemia and a hemorrhagic diathesis which is comparable to that* which occurs in all forms of septicemia

In the years of childhood a characteristic osteochondritis of the centers of ossification of the long bones is sometimes found Instead of the thin line of calcification it is widened and irregular This often gives rise to local pain tenderness and swelling The lower end of the femur is a favorite site Hutchinson s teeth are pathognomonic of congenital syphilis The most obvious deformity is in the central incisors, where a half moon shaped defect on the biting surface is found and these teeth are also frequently peg shaped that is broader at the gum than at the free margin Karnosh who has made a careful study of the histopathology of these teeth, concludes that the true *Hutchinsonian incisor is a deformity of the* developmental lobes of the permanent central incisor and not one of transitory calcium deficiency ' Another characteristic deformity of the teeth is the mulberry shape of the first permanent molar Karnosh has shown that this is due to crests of sound

enamel being on a base of hypoplastic deposit The cusps are generally crowded back on a crown surface of dwarfed dimensions " At puberty there may appear a diffuse hepatitis which may in time progress into cirrhosis of the liver The lesions of the central nervous system are similar to those in the acquired form There may be congenital paresis and tabes dorsalis as in the acquired syphilis and this often appears in the first living member of the family and the subsequent ones may escape Epilepsy and progressive idiocy are not uncommon nor is hydrocephalus which may be suspected as being



Fig 4 5—Photograph f hil l with congenital syphilis showing characteristic changes about the m uth and on the fingers

present when the fontanelle remains open and there is venous engorgement on crying or coughing Other characteristic but less common lesions are syphilitic keratitis syphilitic otitis and optic neuritis

Diagnosis—The diagnosis of the primary lesion in acquired syphilis is as a rule made without difficulty It may be confused with a chancroid or soft sore herpes lymphogranulomatosis cutis or inguinalis or a simple traumatic injury It should not be difficult to differentiate between these as the chancre is so characteristic but it must always be remembered when life syphilitic

signs appear that the site of the original infection may not be detectable All suspicious sores should be examined for the presence of the Treponema and monthly Wassermann or Kahn reactions should be done for at least six months if there is still any doubt Shortly after the initial infection there appears in the blood an antibodylike substance closely connected with the gamma globulin fraction of the plasma It is not yet proved that this is a true antibody It is therefore called a reagin This is not the place to discuss the possibilities of a positive reaction indicating some other lesion but if it be repeatedly positive the diagnosis of syphilis should be maintained until such time as the real cause can be ascertained A greater difficulty in diagnosis is encountered when skin eruptions appear which may simulate some quite benign condition and there is no history of a primary infection A Wassermann or Kahn test should be done in all such cases Of still greater difficulty are those that do not give a history of either primary or secondary lesions but seek medical advice for some visceral or nervous complaint The routine use of a



Fig 4 6—Hutchinson's teeth (Courtesy of Dr George W Wende From Sutton and Sutton Diseases of the Skin)

Wassermann or Kahn reaction in hospital wards has detected many unsuspected cases of syphilis or has clarified otherwise obscure diagnoses If syphilis is suspected and the Wassermann reaction is negative the investigation of the case is not complete until a spinal fluid examination has been done Occasionally where the blood serum reactions may be negative the spinal fluid reactions will be positive In conclusion as to diagnosis it is a safe rule to suspect all conditions which cannot readily be accounted for by some obvious cause as being syphilitic until this possibility has been proved to the contrary while on the other hand it must not be concluded that every lesion occurring in a person with a positive Wassermann reaction is necessarily syphilitic

Course and Prognosis—The course of syphilis differs greatly from person to person In some who are undoubtedly syphilitic neither primary nor secondary signs or symptoms are recorded in the history The fulminating cases of past generations are now infrequent Further an individual may have contracted the infection in the twenties and live to be an octogenarian without any evidences of it except a positive serological reaction which may have been found during a routine examination

Apart from the mortality from congenital syphilis and those who die as a result of the more advanced functional defects of the central nervous system and the cardiovascular system, the death rate is comparatively low. Syphilis can be cured and before serious visceral lesions occur, provided treatment be instituted in the early stages, and be persisted in until a cure can be pronounced.

Treatment.—*Prophylaxis.*—The best prophylaxis is to avoid promiscuous sexual contact. In the past 25 years active prophylactic treatment has been used extensively. Immediately after exposure thorough cleansing of the genitalia with soap and water followed by a generous and extensive application of calomel ointment has undoubtedly been successful in a large number of cases. This would be expected as the treponema is a particularly fragile organism which is easily killed. Therefore it is of the greatest importance that these prophylactic measures should be carried out within a few hours after exposure before the organism has had an opportunity of penetrating the superficial layers of the skin. Congenital syphilis to a large measure can be prevented by doing a Wassermann, Kahn or other specific diagnostic test on all pregnant women before the fifth month. If positive, proper treatment should be immediately started. This will insure the majority of infants born of such mothers being nonsyphilitic.

Curative.—The cure of syphilis rests upon two main principles, thoroughness and persistence. In the acute stages, that is during the period of dissemination of the treponema, it is well to keep the patient in bed, particularly if there is pyrexia. At this time he should have a dental examination and thorough oral hygiene should be instituted in preparation for a probable period of mercurial therapy. He should be reassured that cure is not only possible but almost certain, provided he is obedient. The diet and general regime should be that of any infection and after he is allowed to return to his usual occupation fatigue, overwork and worry should be avoided and in other manners he should lead a normal rational life of abstinence and should be encouraged to take outdoor recreation and a sufficient amount of sleep. In married people a difficult situation naturally arises. This is best handled by frankness on both sides and the physician will often be called upon to be the guide counsellor and friend. It is imperative, however that any chance of cross infection should be prevented and this can best be accomplished and other complications avoided by knowledge rather than by ignorance. Under present methods of specific therapy a patient can be rendered noninfectious in a matter of a few days.

Specific.—As soon as the presence of the infection is recognized active treatment should be begun. A few exceptions to this will be dealt with below. If the disease is in the serological negative stage it is improper to wait until the reactions are positive because it is at this phase that the greatest curative success is to be hoped for. Not only will this be more certain of accomplishment but there will also be a fair expectation that neurological and cardiovascular syphilitic lesions will be prevented. At one time it was considered proper to carry on the treatment in periodic courses. It is now the consensus of opinion that it is much better for the treatment to be con

tinuous This applies where arsenic alone is used, and also where it is alternated with or supplemented by, mercury, bismuth penicillin or chloromycetin

The treatment has rested upon the use of arsenic in the form of neoarsphenamine arsenoxide (mapharsen) the heavy metals, bismuth and mercury penicillin and chloromycetin and potassium iodide The first five are direct treponemacides while the last although having no direct action upon the treponema is of value in promoting the absorption of syphilitic exudate and scar tissue There are a number of other arsenical preparations now in vogue—sulfarsphenamine tryparsamide, etc They each have virtues but are best employed by those who are expert in the treatment of syphilis or have adopted this branch of medicine as a specialty Neoarsphenamine is probably the better arsphenamine as it can be more easily prepared, but on the other hand, it is less constant in its toxicity and somewhat less effective Sulfarsphenamine is used considerably in pediatric practice as in children the intramuscular administration is seldom followed by severe local reactions Mercury, a drug of ancient and honorable reputation is being replaced by bismuth It may be administered either by mouth by inunctions or by intramuscular injection of one of the soluble salts such as the bichloride cyanide oxycyanide or succinimide, or insoluble salts such as mercury salicylate suspended in oil may be given intramuscularly This has a disadvantage of being painful and often gives rise to severe local reactions

Bismuth has become a favorite heavy metal in the treatment of syphilis It is given intramuscularly as a salt such as sodium potassium bismuth tartrate or bismuth subsalicylate The doses of these various chemical treponemacides are given in Table XIX

TABLE XIX

ARSENICALS	BISMUTH	MERCURIAL
Intravenously Arsphenamine weekly 0 2 to 0 6 gram Neoarsphenamine weekly 0 6 to 0 9 gram Sulfarsphenamine weekly 0 to 0 6 gram Tryparsamide 0 5 to 3 0 grams 1 to 2 weeks Arsenoxide (mapharsen) twice weekly 0 04 to 0 06 gram	*Intramuscularly* Bismuth subsalicylate in oil 0 2 gram weekly Na K bismuth tartrate 0 1 to 0 2 gram 3 times a week	*By Mouth* three times a day Mercury bichloride 1/12 grain Protiodide ½ grain Metallic mercury (Blue Pills) 1 gram Hydragyri perchloride (Green's Mixture) 1/12 grain *Intramuscularly* 1 to 2 days apart Bichloride Cyanide Oxycyanide Succinimide 0 01 gram. *Intramuscularly* weekly Mercuric salicylate 0 2 gram weekly *Inunction* daily Metallic mercury (Blue Mass) 1 dram

Penicillin has been found to be an excellent agent in the treatment of this disease It has been given in amounts of 30 000 to 90 000 Oxford units every three hours until 2 to 5 million units have been given It is well to combine it with arsenicals and bismuth It is strongly indicated when the possibility of reactions or hepatic or renal damage is to be avoided as in pregnancy

Potassium iodide in amounts of 10 to 40 grains, three times a day, may be given continuously. There is no reason to omit it even in the earliest cases, and in the older lesions it is often wise to institute a preliminary intensive course of iodide before the treponemacides are started. It should always be administered with large amounts of water.

At the beginning of the treatment the full doses of the chemical and antibiotic treponemacides should not be given but should be started at about one third the usual amount and be gradually increased up to the maximum.

The chemical treponemacides are all toxic drugs. Although they may have a selective action on these organisms, they are not without effect upon the fixed cells of the body. There are certain effects or reactions which should be avoided. These are as follows:

Arsenicals.—1. *Nitritoid Crisis.*—During the administration of an arsenical preparation flushing, tingling of the skin of face, neck, and extremities, with injection of the conjunctiva may be complained of. This is immediately followed by a sense of suffocation and choking, palpitation, and sometimes edema of the lips and face. There may be collapse. These symptoms closely simulate an anaphylactic shock, and have been attributed either to an idiosyncrasy on the part of the patient to this particular arsenical preparation or to faulty technic. As it is apt to recur on each succeeding injection it seems more likely to be due to the former. It is best treated by 10 minims of adrenalin subcutaneously.

2. *Dermatitis.*—The patient should be cautioned to inform his physician if there is any itching of the skin during the course of treatment, as this is the first indication of the onset of an exfoliative dermatitis which may be quite serious not only on its own account but also because it requires a discontinuance of all arsenical preparations and further prevents the use of mercury in the form of inunctions.

3. *Jarisch-Herxheimer Reaction.*—This is characterized by symptoms referable to the central nervous system and seems to be connected with a sudden destruction of the treponema with syphilitic intoxication as there is a temporary aggravation of the symptoms of the disease. It may occur when the principal syphilitic manifestations are in any site. It usually follows after the first dose in twenty-four to forty-eight hours. It is most frequent in chronic cases and in these the amount of the initial injection should be about one quarter of the average dose. It is relatively uncommon in lesions of the nervous system but more common in those of the skin, liver, and heart. The time interval varies considerably. In the nervous system it usually does not occur until the second to fourteenth day. After tryparsamide, it is as a rule delayed until the second or third week.

4. *Hepatitis.*—In some cases arsenic seems to have a particularly toxic effect upon the liver. Therefore the slightest suggestion of jaundice indicates the discontinuance of the drug. In suspicious cases or in those with a history of jaundice or hepatic disturbances it is well to check this matter by the van den Bergh reaction done at regular times.

5 *Aplastic Anemia* —Arsenic has at times what appears to be a specifically toxic action upon the bone marrow, and may lead to a rapid anemia of the aplastic type It is sometimes difficult to be certain whether the intoxication of the bone marrow and the anemia are due to the action of the arsenic or the treponema

6 *Agranulocytosis* —An increasing number of cases are found in the literature where agranulocytosis (see page 564), particularly in women develops during or following the administration of arsenic The connection between these two events is not always clear, but there are sufficient cases reported in which there seems to be a definite connection rather than a coincidence, to warrant sounding a word of warning in this regard

7 *Sudden Death* —This sometimes occurs particularly in long standing cardiovascular and cerebrospinal syphilis in association with some of these reactions but there are other instances where it cannot be accounted for by any of them

8 *Blindness* —Serious visual damage may result from the use of tryparsamide This drug should never be given to patients with preexisting optic atrophy Before starting treatment examination of the fundi visual acuity and visual fields should be carried out The slightest subjective or objective evidence of visual disturbance calls for immediate cessation of treatment

Mercury and Bismuth —These are apt to produce salivation stomatitis diarrhea and nephritis Therefore strict oral hygiene should be insisted upon and the urine examined weekly while these drugs are being given

Penicillin —The toxic reactions are comparatively insignificant and consist of urticaria dermatographism and a clinical picture like serum sickness It must be appreciated that it may produce a Jarisch Herxheimer reaction

The treatment of early syphilis has been a fruitful field in therapeusis and this has been made somewhat more complicated by the introduction of penicillin and chloromycetin as powerful antisyphilitic agents For a time there was considerable controversy waged around the intensity and duration of arseno therapy Short courses with high dosage versus longer periods with smaller doses divided the profession Further there was a difference of opinion as to the time and place for mercury and bismuth Now penicillin and chloromycetin have entered the field In fact the successful treatment of this disease requires such constant vigilence and thorough knowledge of the variations indications and complications which are inherent in the use of these drugs and in the disease itself that it is claimed by many that it should be left in the hands of those who specialize in this disease There is no doubt that they obtain a much higher percentage of cures as compared to those who treat a case occasionally It could be compared to the treatment of tuberculosis In both the early diagnosis is the responsibility of the general physician the treatment that of the specialist

In latent or late syphilis the interval between the time of the original infection and the time the patient comes under observation to some extent determines the line of action If many years have passed (the patient being over sixty five years of age) and there are absolutely no signs of functional or anatomical changes which can be attributed to the syphilitic infection a positive Wassermann may be ignored The other cases should be treated more

along prophylactic lines for the prevention of syphilitic activity than with the hope of completely eradicating the infection The therapy may be less heroic and persistent periodic courses of neoarsphenamine and mercury or antibiotics being given at intervals of a few months The urine should be frequently examined for albuminuria and constant vigilance maintained for the appearance of the slightest jaundice Potassium iodide ought to be given continuously In chronic bone lesions without cardiovascular or cerebrospinal involvement the treatment is similar to the acute cases

Cardiovascular syphilis occurs in inverse ratio to the institution of early treatment and is found in about 10 per cent of all syphilitics, being twice as common in males as in females It is interesting, however, that only about 50 per cent of these cases give a history of a primary infection and one third have complicating neurovascular syphilis Particular caution should be exercised in the treatment of these cases as it is not infrequent for sudden death presumably due to ventricular fibrillation or a Herxheimer reaction to occur or a therapeutic paradox may develop This term is used when there is a rapid depreciation of cardiovascular function or acute congestive failure shortly after antisyphilitic treatment has been started It follows the use of arsphenamine Therefore the drugs best suited for treating these cases are mercury bismuth iodide in small doses penicillin and neoarsphenamine Either of the heavy metals may be combined with arsenic which is best given as neoarsphenamine in doses not greater than 0 1 gm per week but should be continued over long periods Aneurysm aortic insufficiency, or chronic circulatory failure are not influenced by the antiluetic treatment and all have a serious prognostic significance If precordial pain (angina pectoris) is present antiluetic treatment must be used with great caution Arsenic is contraindicated in hepatic syphilis

The treatment of neurovascular and meningovascular syphilis has been dealt with under Diseases of the Nervous System (see page 1063)

The treatment of congenital syphilis in no way differs from that used in adults The mercury may be smeared over the abdomen under a binder or given in the form of grey powder ½ grain three times daily Infants seem particularly tolerant of sulfarsphenamine which may be given in doses appropriate to the age of the patient (see Chapter XIX)

YAWS

Synonyms —Frambesia pian bouba

Definition —Yaws is a specific infection which runs a chronic and recurrent course It is caused by a treponema closely allied to that of syphilis In fact many were formerly of the opinion that these two diseases were due to the same cause but were different manifestations changed by local geographical influences and different reactions of the host Yaws is now considered to be due to the *Treponema pertenue* first described by Castellani It is found in the tropics of Asia Africa Australia and America It is not a venereal disease although it is transmitted by direct contact

Symptoms and Signs.—The incubation period is two to four weeks. The portal of entry is through the skin, and the *primary lesion* is usually on the breast or buttock in women and the extremities in men and children. The exact reason for this distribution is not clear. This lesion is called the "mother yaw," "maman pian," or "boubá madre." It begins as a papule and at the end of about one week it acquires a moist surface with a yellow secretion and a dry crust. It may be multiple and coalesce, forming larger lesions. When the crust is removed there is found a clear cut ulcer with a granulating base.

The primary lesion is accompanied by general malaise, low irregular pyrexia, headache and general muscular pains. The neighboring lymph glands soon become large and hard but do not break down. The primary lesion is indolent but eventually may heal or become a large granulating mass. The general symptoms usually disappear temporarily. The *secondary lesions* indicative of a general dissemination of the spirochete appear in about five to twelve weeks after the primary lesion. There is now a recrudescence of the general symptoms, the pains in the muscles, joints and bones, and headache being especially severe. Small reddish papules appear in the skin. They are widely distributed and persist for many weeks. Some gradually disappear, others coalesce to form large areas with an areola darker in colored races and reddish in white races.



Fig. 4.—Tropical yaws, tertiary stage, showing some rather unusual bone lesions. (Courtesy of Drs. C. L. Pickett and Leta M. Pickett. From Sutton and Sutton, Diseases of the Skin.)

In the tertiary stage there are deep seated gummatous nodules in any tissue but chiefly in the bones and muscles. The *boomerang shin* of the Australian aborigines is held to be due to yaws and is analagous to the sabre shin of syphilis. The viscera are not involved. In the skin the nodules ulcerate and may be extensively destructive. Secondary epithelioma in untreated cases is common.

Pathological Anatomy.—The pathological anatomy is essentially granulomatous, particularly in the secondary stage when there is great thickening of the skin. In the tertiary stage the destructive qualities are the most distinctive.

Diagnosis.—The diagnosis is seldom difficult in endemic areas. The treponemata can be readily found by methods similar to those used in syphilis. The Wassermann reaction is positive so that the differential diagnosis is made on clinical grounds alone, as there is no microscopical or serological test to differentiate syphilis from yaws.

Course.—The course of the disease is protracted, but it does not kill as a rule, although death may be due to secondary infection through the secondary or tertiary cutaneous lesions. It is more disabling than fatal.

Treatment.—The treatment is similar to that for syphilis. Neoarsphenamine first dose 0.3 gram, subsequent ones 0.6 gram with three to five days'



Fig. 478.—Yaws in a young Siamese. (Courtesy of Dr. Ralph Mendelson. From Sutton and Sutton, Diseases of the Skin.)

intervals for six to eight doses is efficacious. Stovarsol, one gram daily, in divided doses by mouth also gives good results. Penicillin would appear now to be replacing the arsenicals in the treatment of this disease. It is administered after the same manner as for syphilis but the amounts required are

much less and the duration of the treatment is shorter, as follows 1 200 000 O U in thirty divided intramuscular doses at three hour intervals or 1 200,000 O U in oil with beeswax intramuscularly in two doses at 24 hour intervals Potassium iodide is to be advocated particularly for the granulomatous lesions By these measures cure is usually assured

LYMPHOPATHIA VENEREUM

Synonyms —*Benign lymphogranulomatosis, poradenitis climatic buba Nicolas Favre disease lymphogranuloma inguinale*

Definition —Lymphopathia venereum is a specific infectious disease It is transmitted by venereal contact and the portal of entry is an inconspicuous primary lesion followed by lymphadenitis suppuration and cicatricial deformities

Etiology —The cause of the disease is a filtrable virus The pus from the lesions contain elementary bodies similar to those found in psittacosis The disease has been experimentally induced in mice, guinea pigs and monkeys

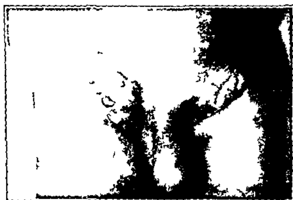


Fig 4 9—Classical lymphogranuloma inguinale Frei test positive (Courtesy of Dr Harold N Cole) (From Sutton and Sutton Diseases of the Skin)

Symptoms and Signs —The disease is transmitted by sexual contact and so is called the "fourth venereal disease" It may, however be contracted by extragenital routes especially through the mouth The incubation period is variable—one to seven weeks, averaging about three weeks The initial or primary lesion is usually an inconspicuous single papular infiltration on the *glans penis* or prepuce in the male It seldom appears on the vulva in the female but when recognized is found on the fourchette It is probably more common within the vagina which may account for the variations in glandular involvement in the two sexes Occasionally the primary lesion may be vesicular or herpetic with erosion while in others it may simulate the chancre of syphilis but is softer and more superficial This primary stage may be accompanied by slight pyrexia malaise headache and anorexia

After two to three weeks the glands in one groin (rarely bilateral) enlarge and become painful At first discrete they soon merge into a large mass The skin soon becomes attached and appears purplish or dark red with signs of

Course—The course of the disease is protracted, but it does not kill as a rule, although death may be due to secondary infection through the secondary or tertiary cutaneous lesions It is more disabling than fatal

Treatment—The treatment is similar to that for syphilis Neoarsphenamine, first dose 0 3 gram, subsequent ones 0 6 gram with three to five days'



Fig 478—Yaws in a young Siamese (Courtesy of Dr Ralph Mendelson. From Sutton and Sutton Diseases of the Skin)

intervals for six to eight doses is efficacious Stovarsol, one gram daily, in divided doses by mouth also gives good results Penicillin would appear now to be replacing the arsenicals in the treatment of this disease It is administered after the same manner as for syphilis but the amounts required are

ifestation of cutaneous leishmaniasis (oriental sore, see page 710) and is men tioned here to draw attention to its distinction from the previous disease The treatment is by antimony salts intravenously given in the form of am monium antimony tartrate

GONORRHEA

Synonym.—Clap

Definition—Gonorrhea is an acute and chronic infectious disease caused by the gonococcus It is most commonly a venereal disease although not neces sarily so The infection may remain comparatively local or become systemic

Etiology—It is due to the gonococcus which is biscuit shaped gram nega tive intra and extracellular diplococcus It will not grow on ordinary arti ficial media but requires special preparations such as meat, peptone brain agar, or those that contain ascitic fluid or fresh blood It also grows best when exposed to a low partial pressure of oxygen There seems to be a variability in viru lence in different strains It is contracted usually through sexual intercourse with an infected person occasionally in newborn infants the eyes may be infected, and young girls may contract it through extrasexual contact with infected towels clothing and bed linen Boys are seldom so infected

Symptoms and Signs—The incubation period is usually four to five days The portal of entry is through the urethra in the male, and the urethra and vagina in the female There is a profuse urethral or vaginal purulent dis charge Therefore the local symptoms differ somewhat in the male and female.

Gonorrhea in the male may cause so little discomfort as to pass unnoticed by the patient who has heard so much concerning the severity of the symp toms On the other hand the urethral inflammation may be severe the dis charge thick and profuse and surrounding penile structures may be so affected as to produce irregular and persistent distention which is exquisitely painful causing penile curvature on erection (chordee) If the infection proceeds into the membranous urethra bladder symptoms—frequency urgency dysuria and tenesmus—may be severe and on micturition there may be a terminal hematuria Invasion of neighboring structures may occur producing cystitis prostatitis with abscess epididymitis orchitis infected phimosis and paraphimosis bala noposthitis Cowper s abscess and parafrenal abscesses When the urethritis is severe or any of these adjacent tissues or the posterior urethra are involved a systemic reaction may occur There is general malaise pyrexia and leuco cytosis but unless there is a systemic infection or a local retention or abscess these are of mild degree The disease may be prolonged and develop into a chronic state This is invariably due to some focus in the adjacent structures which is not draining properly and remains infected This is not only impor tant in the perpetuation of the local condition but also as a source for hema togenous or metastatic spread of the virus Stricture of the urethra occurs at times due to local ulceration and loss of substance with scar formation

Gonorrhea in the female affects the urethra but symptoms referred to this structure are not as pronounced as in the male There may be no urethral symp toms whatever When present there is burning and some pain on urination The

periadenitis and then isolated points of softening appear which rupture, producing multiple sinuses discharging a thin seropurulent fluid In women the same sequence of events occurs but the pelvic and perirectal glands are more commonly affected The true nature may not be recognized although there may be a discharge from the rectum and painful defecation

In distinction to the mild systemic symptoms of onset there develop with the adenitis in most cases a pronounced pyrexia, sometimes as high as 104°F, and prostration There may also be delirium, semi coma and signs of dehydration The pulse is always slow The liver and spleen are enlarged and there is usually a mild general adenopathy An arthritis has also been reported in a fair number of cases There are a slight anemia and a leucocytosis, with frequently a mononucleosis An interesting laboratory finding is a hyperglobulinemia

Cases vary considerably in the intensity of the systemic reaction but in all the adenitis passes into a chronic course of many weeks, months, or even years duration Eventually there is healing with massive and destructive scarring which may lead to rectal stenosis and elephantiasis of the penis and scrotum in the male and vulva and perineal regions in the female

In the rare cases where the portal of entry is through the mouth, the tonsils and cervical glands (unilateral) follow the same course

Pathological Anatomy—The anatomical picture is that of an infectious granuloma with suppurative adenitis and periadenitis There are no specific histological characteristics With healing dense scar tissue produces distortion and lymphatic obstruction

Diagnosis—This disease has to be distinguished from syphilis, chancroids gonorrhea bubonic plague, and other causes of suppurative adenitis This is usually not difficult if the possibility of its occurrence be kept in mind Where as it was at one time considered to be a tropical and semi tropical disease it is now known to have a wide distribution and is yearly being reported from new districts The diagnosis can be established by the Frei test for cutaneous sensitivity which becomes positive at the time the adenitis first appears It must also be differentiated from granuloma inguinale in which however, there is no adenitis

Prognosis—As mentioned above the course is essentially chronic, while the morbidity is great the mortality is low

Treatment—There is no specific cure and perhaps the best procedure is surgical removal of the involved glands before they suppurate On the other hand increasingly good results are being reported with potassium antimony tartrate This is used in the same manner as in schistosomiasis (see page 710) It is most efficacious before suppuration but should also be used even under these conditions Sulfadiazine should also be given (1 gram every 4 hours) in full doses There is little evidence that it affects the virus but rather secondary infections

GRANULOMA INGUINALE

Granuloma inguinale is an infectious disease of the genitalia particularly of the pudenda It is caused by *Leishmania tropica* The lesion is a local main

arthritis the intensity of the pain and tenderness causes the patient to prevent all movement, and fixation in these faulty positions rapidly occurs Suppuration and erosion of the cartilage with destruction of the articulating surfaces sometimes occur and the infection may be so intense as to lead to perforation of the joint capsule with involvement of the skin causing a sinus The periarticular tissues tendon sheaths and tendons may be also involved independently of the joint but with perforation of the joint capsule infiltration of the periarticular tissues and the contiguous structures may lead to more extensive local incapacity and joint fixation It is during this period that the surgeon sees the case in order that the suppurating joint may be drained This should be delayed as long as possible as what may seem like a purulent destructive lesion makes a remarkable recovery although there may be some distortion The chronic fixed deformities are those seen by the orthopedic surgeon, but even in these it is surprising what a good result may be obtained by gently breaking down adhesions under an anesthetic and putting the joint in a proper position If this manipulation is delayed too long fixed fibrous and even bony ankylosis may result from this neglect

The ophthalmia which is caused by the gonococcus may be by direct contact of the conjunctiva during birth through an infected canal This, however comprises but a small percentage of the ophthalmic cases Many others result from metastatic infections via the blood stream in the same manner as gonorrheal arthritis These cases chiefly cause an iridocyclitis as well as a conjunctivitis and in some panophthalmitis may ensue They are not common but are destructive and simulate the ocular lesions of tularemia

The endocardium (see page 413) has been reported by Thayer to be the site of ulcerative endocarditis in 7 per cent of such infections This is undoubtedly too high as his cases were largely drawn from a population with a high percentage of gonococcal infection The average incidence is probably about 3 per cent of cases of ulcerative endocarditis This condition has been dealt with elsewhere

The skin lesions are of two kinds namely the local condylomata acuminata which are small papillary growths upon the external genitalia in women which are bathed in the copious and irritating gonococcal discharge from the urethra and vagina They are principally the result of lack of cleanliness The other dermatological manifestations are due to a systemic spread of the virus They may occur with or without an endocardial lesion There have been described erythemas and erythema nodosum which are not particularly characteristic of this infection There are however certain hemorrhagic and bullous pustular eruptions which are quite suggestive They are undoubtedly embolic and closely simulate the severe skin manifestations of meningococcal infections But almost specific are the lesions with hyperkeratosis They are supposed to be rare but undoubtedly they are often overlooked They may be associated with or follow an arthritis As they are due to a bacteriemia this is to be expected They suddenly appear on the palms of the hands soles of the feet and about the nails There are scaly efflorescences with little or no reaction but the whole cutaneous sole palm or nails may be separated

meatus is reddened and pouting and exudes a thick yellow pus On palpation through the vagina it is tender, and may be felt as a firm band beneath the vaginal mucous membrane The inflammation may extend to the bladder and cause cystitis with frequency and urgency The discharge from the urethra rapidly diminishes until it may disappear except when the urethra is milked a small quantity of pus may be expressed As in the male, a chronic urethritis is common but it rarely leads to stricture

Although the vagina may contain considerable pus it is seldom actively involved, as the vaginal epithelium is resistant to the organism The cervical canal is, however a common site for a severe and resistant infection, and from here there is a creamy leucorrheal discharge Skene's and Bartholin's glands are also common sources of persistent infection and an abscess or a cyst may be formed The bladder endometrium, endosalpinx, ovaries, pelvic peritoneum, and pelvic tissues may be involved Gonorrhea is the most common cause of chronic inflammations of the female pelvic organs, and an equally important cause of sterility The symptoms apart from a leucorrhea are vague but persistent There is pelvic pain, low back pain and general debility, while locally the pelvic organs are fixed and painful on examination An acute infection usually reveals the acute inflammatory reaction already described but the chronic infections are less distinctive and often require careful and expert examination to prove their identity

Systemic infection by the gonococcus is relatively uncommon, but when it occurs it is serious As in syphilis the inguinal glands may become enlarged and suppurate, causing a bubo which may ulcerate through the skin and cause a sinus The gonococci may, however, pass through these glands without producing a local adenitis A general infection usually occurs during the period of acute genitourinary infection but not necessarily so in fact metastatic lesions may develop with little or no evidence of persisting local disease The gonococcus has a particular selective action on the synovial membranes of the joints and tendon sheaths, the eye, the endocardium and the skin

Gonorrheal arthritis is the most common lesion resulting from a systemic infection It usually is polyarthritic affecting principally the larger joints At one time it was considered that it differed from rheumatic fever in that the arthritis was not fleeting in distribution This is quite an erroneous conception having arisen from the fact that minor pains and aches with some swelling may be so transitory as to pass unnoticed, particularly if one or more joints are severely involved After the general arthritis has persisted for a few days, there may be pronounced swelling of one or several of the larger joints with redness intense pain fluctuation, and characteristically exquisite tenderness The patient often cries out with pain even when the bed is approached the bedclothes touched, and of course when the limb is moved The emotional disturbances are more extreme than would be expected and are characteristic of this infection The limb is held in a position of semiflexion when the knee or elbow is affected, the foot is extended when the ankle is involved and the leg is rotated outward and flexed when the hip is involved These are the positions usually assumed in any arthritis of these joints but in gonorrheal

ovaries and pelvic cellular tissues The gonococci may not be demonstrable, but with alcoholic or sexual excesses a recrudescence may occur *It is therefore prudent not to be too certain of a cure* and the patient should be duly impressed with the seriousness of the condition Gonorrheal arthritis usually completely recovers without permanent disability, although there is no doubt that some cases are eventually classified as arthritis deformans Endocarditis is often fatal The ocular lesions may cause permanent disabilities and are a common cause of blindness

Treatment —*Prophylaxis* —There is no true immunity to the gonococcus but the infection may be prevented if certain precautions are taken The first is obviously the avoidance of sexual connection with infected persons Secondly, if it must be then prophylactic measures should be promptly used

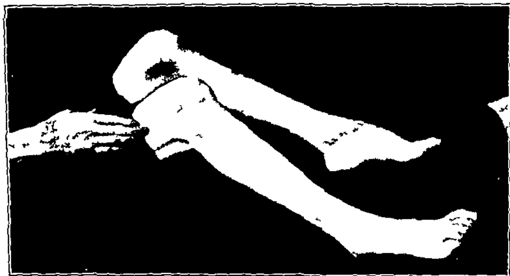


Fig 480 —Photograph of a case of gonorrheal arthritis and of gonorrheal hyperkeratosis of the hands and feet.

These consist of thorough washing of the external genital parts with soap and water and the injection into the urethra of 5 c c of 10 per cent argyrol or other selected antiseptic which should be retained for five minutes This should be done as soon as possible but even up to twenty four hours it has been known to be effective This should be followed by a generous application to the external genitals of 30 per cent calomel ointment to prevent syphilis The prophylactic use of sulfadiazine has had a considerable vogue There is evidence that it is somewhat successful but if used constantly there is also evidence that resistant strains of the organism develop

Active Treatment —There is probably no disease where more harm has been done by rough methods of so called cure as in gonorrhea This organism can only penetrate the more delicate epithelial coverings and anything which injures these promotes further extension of the infection Therefore the local treatment should be gentle and not directed toward actual disinfection but rather local removal of the exudate The best treatment is local and general

and beneath leave denuded surfaces which lead to additional keratosis It is not analogous to a syphilitic lesion, as there is undermining and massive partial separation

The other metastatic lesions are comparatively rare and it is inconclusive whether they are due to the *gonococcus or secondary infections There may be* pneumonia, pleurisy, albuminuria, polyneuritis, meningomyelitis, neuritis and myositis The local bone lesions associated or not with arthritis form an interesting group, namely, osteitis, periostitis, chondritis and perichondritis, and have been connected with gonococcal infections In fact the gonococcus as an hematogenous infection may produce a most diverse collection of lesions

In addition there may be distant local lesions in the anus and rectum, particularly in women The anal lesions are of little importance except for fissures, while a proctitis may vary from a mild catarrh to severe edema, ulceration and tissue necrosis leading to rectal stenosis

Pathological Anatomy—It is characteristic of the gonococcus that it flourishes best in tissues covered by columnar epithelium In the primary infection it invades the intracellular spaces and there produces a powerful endotoxin when it disintegrates There is a great infiltration of leucocytes into the tissues which leads to a desquamation of the epithelium There may be destruction of tissue, and fibrosis in the genitourinary tract In the joints the suppuration and necrosis may be excessive, and in the endocardium there is also great destruction of tissue with exudative polypi

Diagnosis—The diagnosis of the local urethral or genital lesion rests upon the well known primary symptoms and the demonstration of the gonococci This may require most meticulous examination before a definite diagnosis is made and if there be any doubt a specialist's opinion may be necessary In the acute attacks in the male this is seldom required In the female diagnosis may not be so easy particularly as the acute external signs are often transitory In the more chronic cases a thorough and careful examination is necessary In the male careful massage of the prostate and urethra after preliminary superficial washing may reveal a small amount of exudate in which pus and intracellular gram negative biscuit shaped diplococcus may be found This is strongly suggestive but not absolute unless the organisms are grown on artificial media In women chronic gonorrhea is more difficult of diagnosis as the pelvic lesions may result from postpartum infection in the nulliparous these are however practically pathognomonic The gonococcal fixation test if positive is indicative that this infection has occurred in the past but does not necessarily render an absolute verdict unless the other clinical findings would indicate it

The diagnosis of the systemic or metastatic lesions depends upon a careful analysis of all the clinical facts available substantiated by bacteriological and serological evidence There is probably no infection where the local findings have such a diagnostic significance

Prognosis—The eventual result depends upon an early diagnosis and prompt treatment The acute urethritis can usually be cured within a few days But there is a residue of cases that progress to chronic and indolent infection of the prostate, urethral glands seminal vesicles the endometrium,

Etiology—The *Bacterium tularense* or *Pasteurella tularensis* is a short aerobic, nonmotile bacillus which stains gram negative It does not form spores, and in old cultures many coccoid forms may be found It grows best in media containing 0 1 per cent cystin The disease has been reported in nearly every state in the Union and a few scattered areas in Canada It occurs equally in both sexes although men, as will be seen are more prone to be infected than women and both more than children Negroes are less susceptible to infection than whites

Method of Transmission—It is spread from one rodent to another by the Chrysops discalis which is a biting insect with a wide distribution Other mites, ticks, lice, etc, which are parasitic to these animals also play a part in its transmission from animal to animal, and they can transmit the infection to man if they attack him The bedbug also has been accused as a vector



Fig 481 —Primary lesion of tularemia, involving right index finger after repeated surgical incisions. Nodular lymphangitis overlying metacarpophalangeal articulation. Photograph taken six weeks after onset. (Courtesy of Doctor Walter M. Simpson From Sutton and Sutton Diseases of the Skin)

There is a different prevalence for the transmission of the disease to man in different parts of the country In those parts where men are exposed to bites of ticks this is a fairly frequent method of transmission But the most common manner of infection in man is direct inoculation through the skin in those employed in skinning or dressing rabbits In the West the jack rabbit is most responsible, while in the East it is the cottontail Those working in laboratories with this organism are also frequently infected and it has been contracted by those dressing wounds so infected

Symptoms and Signs—The incubation period is one to seven days the average being three and a half days after exposure The onset is sudden with a chill and pyrexia with prostration general pains malaise and headache and the other signs of an acute infection

rest with a diet free from urinary irritants such as coffee, tea, meat extracts condiments, alcohol, and irritating drugs Copious fluid intake, simple diet and continence are imperative

There is no specific serum therapy for this infection Sulfathiazole and sulfadiazine (Chapter XX) have been advocated for both the primary and the secondary lesions In regard to the arthritis and ophthalmic lesions the results with sulfadiazine continue to be most encouraging while penicillin has given results in both acute and sulfa resistant cases that are almost phenomenal (see Chapter XX) Conservative and symptomatic treatment must not be neglected In arthritis, the joints most affected should be kept in an optimum position and when the acute infection has subsided adhesions should be broken down under an anesthetic This may produce a secondary reaction which should then be allowed to subside also In a fortnight passive movement should be instituted and gradually active movements In the meantime local applications of heat and proper splinting to avoid strain and subluxation must be undertaken to prevent deformities Careful manipulations without trauma are usually successful in producing a thoroughly useful joint even in severe local infections Hyperthermia therapy by well controlled methods is an important aid in all forms of gonococcal infection and until recently was the only hope in the treatment of the chronic forms but penicillin would seem to supplant this laborious method

Gonococcal endocarditis was at one time considered incurable But cases are now being reported as cured with penicillin alone or in combination with sulfadiazine Ophthalmic lesions should be cared for by an oculist as more harm than good results from improper measures, and each case is a law unto itself At first instillation of 5 per cent argyrol or other mild antiseptic or irrigant may control the condition, but it must be remembered that the lesion is more often hematogenic than due to direct infection Therefore external therapy except hot or cold applications is usually of no avail Foreign protein shock, particularly with milk proteins, has given good results This brings up the question of such therapy and specific vaccines for the other gonococcal lesions There is no doubt that good polyvalent or autogenous vaccines when used in a proper manner give encouraging results General reactions should not be produced as these have a broader effect than for the immediate lesion Their use is an open question among most specialists The chronic pelvic lesions in both the male and female are really in the realm of urologists and gynecologists, and rough interference and therapy often do more harm than good There are two important points which should always be impressed upon the patient, namely, absolute abstention from alcohol and sexual intercourse until all signs of infection have been absent for some months

TULAREMIA

Synonym —Ohara s disease

Definition —Tularemia is an acute specific infectious disease due to the *Bacterium tularense* which is transmitted to man usually from rabbits or from ground squirrels mice or other rodents There is a characteristic primary cutaneous lesion with enlargement of the neighboring lymph glands

carditis and peritonitis Meningitis has also been reported Increasing numbers of cases of lobar pneumonia bronchopneumonia and bronchitis are being recognized not as primary infections but secondary to the cutaneous lesions

Diagnosis —In a typical case there is little difficulty as the characteristic ulcer and regional adenopathy are so distinctive A chancre on the finger with enlarged epitrochlear glands may simulate it but should be easily differentiated both clinically and serologically The most trouble in diagnosis occurs in the small number of cases where the primary sore has not appeared or has been overlooked The so called typhoid type must be differentiated from typhoid fever paratyphoid fever *miliary tuberculosis and malaria* while the glandular type may imitate Hodgkin s disease infectious mononucleosis or acute lymphatic leucemia The bacteriological and serological examination of the blood absolutely confirms the diagnosis Agglutinins in high titer appear early in the disease The only precaution to be remembered is that occasionally there is cross agglutination with *B abortus* and *B melitensis* An intradermal test is now available

Course —The course of the disease is irregular the pyrexia usually lasting from three to four weeks The immediate *prognosis* is good the mortality being on the whole under 5 per cent, although in small series it has been reported as high as 15 per cent The convalescence is tedious as there is considerable physical and mental depression for many weeks or even months

Treatment —*Prophylaxis* among those who handle rabbits in infected areas is of the utmost importance It is during the dressing of these animals for food either in the home or for consumption in the general market, or when skinning them for the fur market that many are infected This is prevented by wearing gloves In areas where infected ticks and other biting insects which are vectors abound the problem is more difficult In laboratory workers even the utmost precautions are sometimes of no avail

The patient should be treated along symptomatic lines as in all acute infectious diseases The sulfonamides and penicillin have been used with indifferent success but the results with streptomycin are most encouraging (see *Chapter XX*) This has been used both intramuscularly and by local application particularly in eye lesions Excellent results would also seem to be obtained by the use of bismuth sodium tartrate intravenously (*2 per cent solution*) Oxygen therapy may be indicated when pneumonia is present and suppurative pleurisy and peritonitis may require operative interference The glands should never be incised if it can be avoided A suppurating gland should be left alone as long as possible with the hope that the general infection will subside before incision is absolutely necessary

ANTHRAX

Synonyms —Wool sorter s disease malignant pustule charbon milzbrand

Definition —Anthrax is a specific acute infectious disease transmitted to man by direct contagion through the skin and mucous membrane

Etiology —It is caused by *B anthracis,* which is a rather large gram positive, nonmotile bacillus which grows readily in heaped up bunches of filaments on solid media The growth has been likened to 'doll s hair " It was

The primary lesion is most frequently found on the hands or fingers This is a shallow ulcer which is covered with a greyish membrane, and exudate is not abundant It is indolent in healing The virus apparently proceeds from the primary sore via the lymphatics to the lymph glands which rapidly become enlarged and painful Their size is greater than would be expected and draining into and connecting them reddish purple lymphatic channels are visible This reaction may be so intense as to cause a widespread lymphangitis Occasionally cellulitis and suppurative adenitis occur Although the first regional glands as the epitrochlear are most enlarged, the second line, as the axillary, are also commonly affected This has been called the *ulceroglandular type* and accounts for the great majority of the cases

If the eyes be rubbed by hands upon which there is infected material the conjunctiva becomes the site of the primary lesion and the regional glands are likewise affected This is called the *oculoglandular type*, but in no way except for the position of the primary sore does it differ from the so called ulceroglandular variety In fact it would seem an artificial distinction to differentiate them A multiplicity of types of syphilis depending upon the site of the chancre could with equal reason or unreason be so differentiated The conjunctiva is intensely congested and edematous with pronounced photophobia and lacrimation Keratitis may also be present

In 85 per cent of the cases the portal of entry can be identified and the regional glands are occasionally not enlarged In the other 15 per cent the portal of entry cannot be located In some there is a pronounced general adenopathy and these have been classified as the *glandular type* The remaining cases have presented no conspicuous glandular enlargement and have been called the *typhoid type*, these usually occur among laboratory workers The exact method of infection in these cases without a detectable primary lesion is still a matter of doubt The following suggestions have been made—ingestion inhalation or via the skin without producing a local lesion This is further substantiated by visceral lesions such as the following

Pleuropulmonary tularemia produced by inhalation of the organism The onset is fairly abrupt with nonproductive cough dyspnea fever malaise and pleural pain is prominent It differs but little from the secondary lesion mentioned below It is usually only recognized by finding the specific bacterium isolated from mice inoculated with sputum

Gastrointestinal tularemia results from ingestion of the bacterium usually through eating undercooked rabbit meat heavily infested There may be produced a severe necrotizing lesion in mouth pharynx and nasopharynx with enlargement of the neighboring glands Nausea vomiting and severe abdominal cramps with diarrhea may follow Cases are reported with a fulminating course particularly in children

The general features of tularemia are an irregular fever seldom above 104° F, usually about 102° resembling that of sepsis Repeated chills are common There is tachycardia in proportion The spleen is enlarged and frequently palpable as is also the liver There is a mild polymorphonuclear leucocytosis (35 thousand have been reported in occasional cases) The visceral lesions are principally in the serous cavities producing pleuritis, peri

which may be confirmed by finding the anthrax bacilli in the scrapings of this and by the Ascoli reaction This is a simple precipitin test a small amount of the infected material is mixed with 5 to 10 c c of salt solution, and when this has been filtered and cooled, it is poured upon a precipitating serum A *white zonelike ring forms which is characteristic of the infection* It is an important supplement to the bacteriological examination

Prognosis —The prognosis is always serious, especially when the portal of entry is on the face or neck, or through the respiratory system, when the course is extremely rapid death occurring *usually within forty eight hours* On the other hand if the primary lesion is on the hand or arm, a longer period elapses before a general infection occurs and during this period much may be done



Fig 482 —Anthrax. Infection f o n shaving brush (From Sutton and Sutton Diseases of the Skin.)

Treatment —Prophylaxis is naturally most important This may be approached by sterilization of skins and hides which may be infected, and the vaccination of cattle sheep and human beings who may be exposed to the infection through environment or contact Curative treatment is difficult when the primary lesion is on the face or neck or through the gastrointestinal or respiratory system The principal hope is when the primary lesion is on the hand or arm No time should be lost in giving massive doses of anti anthrax serum Penicillin has produced an excellent response in the small number of cases so far reported It should be given in full doses of 480 000 O U in 24 hours (see Chapter XX) combined with antianthrax serum Local surgical procedures have been discarded as they frequently change a local into a general infection Irrespective of what treatment is used, success depends upon an early diagnosis

GLANDERS

Synonyms —Farcy equinia, malleus

Definition —Glanders is an acute or chronic infectious disease due to the *Malleomyces mallei* and is contracted by man from horses mules and other equina through the skin and mucous membrane

one of the first organisms to be identified with disease It forms spores which are extremely resistant to heat and ordinary disinfectants They persist in the soil for a long time and are distributed in pastures and other areas by the excreta of infected animals or from their dead bodies even when buried All animals, including man, and birds are susceptible but it is more commonly found in cattle and sheep

Symptoms and Signs—In cattle, sheep, and other herbivorous animals the *infection gains entrance through their food being contaminated by spores* of the bacilli In man it may gain entrance through the inhalation of dust as in wool sorters when sheep's wool is infected There have been reported cases infected through biting insects carrying the bacilli and inoculating them through skin abrasions Water borne infection has occurred when the refuse and washings of infected hides, etc, have been washed down a water shed to infect wells or other sources of drinking supply But the most important portal has been through casual skin cuts or abrasions by those handling hides or using cheap shaving brushes which harbor anthrax spores

The incubation period is twelve hours to two days The primary lesion is usually on the face or hands It begins as a small red area like an insect bite which soon forms a vesicle with surrounding induration and edema There soon develops a black gangrenous center with spreading edema and adjacent crops of vesicles which coalesce and eventually form a rather large, hard, indurated and necrotic area from which a slough separates hence the name malignant pustule There is no suppuration The neighboring lymph glands in a few days become enlarged The general symptoms are moderate pyrexia head ache nausea and general muscular pains The pulse is weak and rapid with great prostration and collapse There are few localizing symptoms in this general systemic infection

When the bacilli are ingested, there are the usual systemic symptoms and in addition the whole gastrointestinal tract from the nose and nasopharynx to the rectum is intensely congested and hemorrhages occur from the mucous membranes Intense bloody diarrhea and hematemesis are common *Visceral* lesions sometimes also occur and are called internal anthrax In this form there are few or no distinctive features

In spite of the malignant character of the disease the patient has little or no pain nor is conscious of the seriousness of his condition and death may occur within forty eight hours, especially if the portal of entry is via the face or eyelids In the respiratory form of the disease when there is laryngeal tracheal, bronchial and pulmonary infection there is intense congestion and rapid systemic dissemination with cerebral symptoms collapse and death Pneumonic signs may develop but these are rare due to the fulminating char acter of the infection

The *pathological anatomy* is principally an intense necrosis or in the more areolar tissues edema is the dominant feature The local lesion is practically the only one which is characteristic of the disease and if not recognized the true pathological process may be overlooked

Diagnosis—The diagnosis rests entirely upon the recognition *of the possi* bility of an anthrax infection through the character of the primary lesion

sometimes difficult on account of their small numbers Strauss has introduced an important diagnostic method If some of the pus or hemorrhagic discharge from an ulcer be injected into the peritoneum of a guinea pig an acute purulent orchitis will develop after twenty four to thirty six hours from which the *M mallei* may be readily isolated

Prognosis—The course of glanders varies a great deal In the acute variety death usually occurs within a short time from pneumonitis or general sepsis In the chronic form it may last for many years particularly if the lesions remain superficial and the viscera are not involved

Treatment—*Prophylaxis*—As the disease is contracted from an infected horse or other equines these should be destroyed as soon as detected and their stables harness blankets and drinking buckets and troughs disinfected

The *treatment* of an active case is principally symptomatic The local abscess should be treated surgically and with the thermocautery The general regime is that of an acute or chronic infection comprising rest, good diet fresh air, and fluids Specific treatment has been unsatisfactory Vaccine therapy has been advocated as has also injection of mallein but the benefits are indefinite Many drugs have been used, such as mercury inunctions, creosote potassium iodide, sodium benzoate internally, iodine, ichthyol, phenol with alcohol hydrogen peroxide boric acid and potassium permanganate locally Their number indicates the dubious benefit of any

TETANUS

Synonyms—Lockjaw, trismus

Definition—Tetanus is a specific infectious disease caused by the *Clostridium tetani* which produces toxins with a close affinity for the central nervous system leading to local and general tonic spasms

Etiology—The *Cl tetani* is shaped like a drumstick with a spore at one end There are nonspored forms which have rounded ends and are actively motile It is gram positive and absolutely anaerobic and is found in the soil It has a natural habitat in the intestinal tract of herbivora who spread the infection by their droppings The distribution and concentration of the organism in the soil vary considerably in different parts of the world

It gains entrance to the body through wounds, particularly penetrating ones such as those due to a nail or other sharp object, gunshot or shrapnel wounds especially when infected cloth is carried in with them Operations about the rectum or perineum are occasionally a portal of entry as are also dirty vaccination wounds Rarely a case develops without any history of injury These are supposed intestinal infections There is a high incidence of the disease in July due to the entrance of the bacilli through burns from fire crackers but it is most common in the summer months and in warm climates as compared to the winter and arctic regions

Symptoms and Signs—The incubation period is from one to three weeks and depends to some extent upon the situation of the portal of entry If it be in the distal part of an extremity it is longer than when in the face or neck There are no symptoms at this time and the wound may have been forgotten,

Etiology—It is due to *M mallei* which is usually a straight rod shaped organism, although occasionally it is slightly curved It measures 3 to 4 microns in length, and 0 5 in width It is nonspore bearing and nonmotile, and stains easily but irregularly, giving a beaded appearance, and is gram negative It grows easily on artificial media, particularly potato, where it forms a slimy growth which gradually changes from a yellowish to dark red dish brown color

Symptoms and Signs—The incubation period of glanders may range from three days to four weeks The portal of entry is through the skin, and the disease is chiefly contracted by those occupied with horses, particularly farmers, hostlers, grooms and stableboys The onset may be either acute or chronic

Acute glanders begins with malaise, headache, nausea, vomiting and general pains There may be chilliness, but seldom rigors, with an irregular pyrexia In some cases the onset is more violent and the symptoms are those of a respiratory infection closely simulating pneumonia Arthritic signs may be a prominent feature suggesting acute rheumatic fever A fourth group for a time have no localizing signs and imitate typhoid fever, miliary tuberculosis or subacute bacterial endocarditis After a few days skin abscesses appear with an intense local reaction, and from them there is a spreading lymphangitis along the course of which small hard nodules or "farcy buds" develop Similar abscesses may appear on the mucous membranes of the nose, pharynx and larynx, and in the lungs and pleura In all there is necrosis with suppuration The lesions in the skin may be so numerous as to suggest smallpox

Chronic glanders has an insidious onset without general symptoms There appear, first on the skin usually of the hands arms or face, one or more nodular swellings which suppurate become necrotic and form an indolent ulcer from which there is a sticky discharge The ulcers are usually multiple They may heal, but it is the rule for others to develop locally or at a distant site The infection may remain dormant for years and then reappear The mucous membrane of the nose and nasopharynx is a favorite site for chronic glanders to persist, resembling a chronic nasal catarrh with mild local signs and no constitutional symptoms

Pathological Anatomy—Although the *M mallei* usually gains entrance through the skin or mucous membrane, the diffuse lesions are hematogenous and abscesses may be found in the lungs pleura, larynx liver spleen, muscles, bones, and joints The lesion is between a tubercle and an abscess The nodules are dense collections of epithelioid cells and leucocytes They soon undergo necrotic disintegration and liquefaction with the formation of irregular ulcerations which heal slowly forming raised scars as in syphilis

Diagnosis—The diagnosis of glanders is often difficult With the reduction in the use of the horse as a beast of burden it has become a comparatively rare disease The character of the nodules and ulcers might suggest syphilis or tuberculosis, while the systemic symptoms require its differentiation from rheumatic fever pneumonia miliary tuberculosis typhoid fever etc The finding of the *M mallei* in the pus makes the diagnosis complete but this is

neurosis with hyperventilation which, producing an uncompensated gaseous alkalosis and severe tetany, is easily confused with tetanus An absolute diagnosis may be made by finding the *Cl tetani* in the tissues at the portal of entry even though it has seemingly healed

Course—The course of the disease varies somewhat There are patients in whom the symptoms remain localized in one area and may develop many weeks after the initial lesion In these the infection has been small in amount or for some reason the bacilli have been in an indifferent tissue environment Some of these recover If general symptoms develop before specific treatment has been started the death rate is practically 100 per cent, while if specific treatment has been given and symptoms then occur they may be mild with recovery This, however, is not always the case as some progress to a fatal issue It is not unusual for symptoms to develop many weeks after the initial infection, in fact a piece of shrapnel imbedded in tissue may harbor the bacilli and when an attempt is made to remove it tetanus may ensue due to the aggravation of the local infection

Treatment—*Prophylaxis*—Every suspicious wound which means those received in warfare from firecracker burns from penetrating wounds about barnyards or on the public streets should be thoroughly cleansed, extirpated and exposed to oxygen by either free access of air or pure oxygen, and specific *antitoxic serum should be immediately administered Protection before injury* may be afforded to gardeners blacksmiths cattlemen and soldiers by the periodic prophylactic injection of 1 500 units of antitoxic serum in four weekly doses This however is of temporary benefit (18 months) and may lead to a false *security Active immunity by the injection of an anatoxin toxoid is relatively* permanent

If prophylactic protection has not been given 50 000 units of tetanic antitoxic serum should be injected intravenously and an equal amount intramuscularly as soon as the first sign or symptom appears These amounts should be repeated daily until there is a definite reduction in spasms and then every other day until these cease Others advocate 200 000 units (one half the total dose given intravenously and one half intramuscularly) the first day and repeating in amounts of 80 000 units daily In the meantime the tonic and clonic spasms should be controlled by the intravenous injection of 50 c c of a 20 per cent solution of magnesium sulfate as often as is necessary to control them It is not curative but palliative to reduce the colossal expenditure of energy caused by the spasms Many other drugs have been advocated for the same purpose such as curarine and ethylenediamine A moderate anesthetic state obtained with avertin or allied drugs is probably the best method of reducing the effect of external stimuli In addition to all such therapy the patient should be kept absolutely isolated from all external stimuli in fact, should be kept metaphorically *wrapped in cotton wool The greatest difficulty is a food supply* A continuous intravenous injection of glucose and amino acids or a balanced liquid diet given by an indwelling gastric tube through the nose over days is sometimes the only rational method Both require constant attention however Hydrotherapy for the control of pyrexia may be used but at this stage the end is not far off

when there is felt a stiffness in the opening and closing of the mouth and a sense of apprehension and restlessness with frequent yawning There may then be some discomfort at the site of the wound

After a few days the tonic spasms of the masseter muscles become so strong that the mouth cannot be opened and attempts to do so cause exquisite pain The spasticity rapidly spreads to other muscles of the face and neck The face has a perpetual grin or grimace and there may be opisthotonos The patient becomes intensely sensitive to all external stimuli which now produce clonic spasms, and this is called the hyperesthetic stage These clonic reactions may be local or general They occur with increasing frequency and from the slightest stimulus such as a noise, an increased light, a current of air, or the slightest touch to the bed or bedclothes The diaphragm may be particularly involved and seriously interfere with respiration

During the second week of symptoms the terminal stage usually develops The pain is now intense, there are urinary retention, pronounced pyrexia, sometimes hyperpyrexia, sweating, exhaustion and death The ghastly feature of the termination is the mental alertness of the patient to the end

With the increasing intensity of the tonic and clonic spasms the muscular energy expended demands a greatly augmented supply of oxygen, so although true basal oxygen demands cannot be estimated the oxygen consumption may rise to tremendous amounts There is a parallel heat production which can not be dispersed and in consequence the body temperature rises There is also a pronounced tachycardia not due to a direct intoxication but to the demands of an excessive and constantly increasing blood flow per minute The systolic blood pressure rises as in physical exercise, but toward the end falls from exhaustion and cardiac failure Otherwise physical examination is negative

Pathological Anatomy—The pathological anatomy of tetanus is not specific There may be some degenerative lesions of nerve cells and petechial hemorrhages in the brain and cord *There is no evidence that these are in* any way specific The *Cl tetani* produces two toxins tetanolysin and tetanospasmin The latter produces the picture described above It is taken up by the motor end plates in the tissues of the portal of entry and ascends along the axis cylinder or lymphatics of the nerves to the motor ganglia of the cord and brain The manner of its effect is not agreed upon There are two contentions, (a) that the tetanospasmin renders the nerve cells more sensitive to stimuli and (b) that it removes the power of inhibition so that there is an unchecked response to slight stimuli which normally would be compensated for

Diagnosis—This disease may be confused with strychnine poisoning rabies, tetany, meningitis and hysteria but the history and suitable examinations should readily clarify the picture The first can only be suspected by the immediate history of accidental or suicidal administration of the drug Rabies follows a dog bite It is true that many weeks or months may have intervened A lumbar puncture proves or disproves meningitis Tetany and hysteria give greater difficulty particularly in the first attack of a respiratory

Fig. [illegible]—[illegible] typical. (Courtesy of Dr. [illegible]. From Sutton and Sutton, Diseases of the Skin.)

FOOT AND MOUTH DISEASE

Synonyms —Epidemic stomatitis, aphthous fever

Definition —Foot and mouth disease is a specific infectious disease of cloven foot animals (especially cattle, sheep, and pigs) and man It is caused by a known filterable virus and is characterized by vesicles appearing on the mucous membrane of the mouth, pharynx, lips, and the skin between the fingers and toes It is contagious

Symptoms and Signs —The incubation period is between four and ten days, and the portal of entry is through the skin of the hands or the mucous membrane of the mouth and lips The onset is fairly sudden with general malaise, headache, vomiting and pyrexia There is diarrhea at first and then constipation After a few days (three to eight) there is felt a burning sensation of the hands, feet and mouth The former show a transitory exanthem while the mouth and lips are intensely red Soon small vesicles appear on the mucous membranes and sometimes between the fingers and toes (Figs 483 and 484) The vesicle is yellow with a red areola and at first contains clear fluid which becomes turbid, and it finally breaks leaving a shallow ulcer Those on the skin become dry and scaly They all heal without scarring The mouth is sore and mastication is painful The tongue is heavily coated with a slimy film and there is profuse salivation and the breath is fetid The disease terminates in about three weeks in recovery

Diagnosis —This disease is to be differentiated from herpes, pemphigus and other forms of aphthous stomatitis The distribution of the eruption excludes the first the presence of fever the second and the constitutional reaction and lesions on the fingers and toes the third The diagnosis is confirmed by guinea pig inoculation and the demonstration of the presence of the virus by cross immunity reactions

Treatment —Strict isolation is imperative and those working with infected animals should take every precaution to avoid contamination Milk from such cattle should be discarded or boiled before using and never fed to pigs The individual case is treated by general symptomatic measures The mouth should be frequently irrigated with a bland antiseptic solution in large quantities and to painful ulcers silver nitrate should be applied

INFECTIONS DUE TO THE BITES OF MAMMALS

Human beings are not infrequently bitten by other human beings dogs cats, horses camels rats etc The majority of these injuries produce no other lesion than that due to pyogenic or necrotic organisms Probably the worst of such are those due to the human bite when a foul infection due to the organisms of dental caries and pyorrhea produces an indolent, sloughing wound In addition to these there are two specific infections transmitted by mammalian bites which in themselves are locally comparatively clean but the general dissemination of the virus produces most profound and specific results They are rabies and rat bite fever

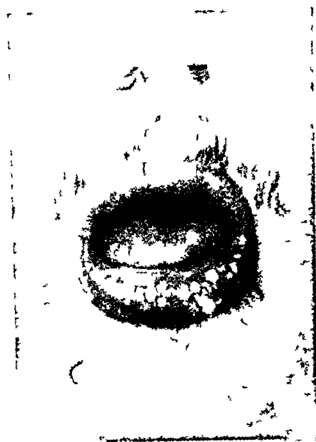


Fig. 45[illegible].—Foot and mouth d[illegible] The [illegible] d[illegible]tribution [illegible] th[illegible] are typical (C[illegible] of Dr Paul W [illegible]) From Sutton and [illegible] Disease [illegible] the Skin)



Fig 484—Foot and mouth disease in man showing character and distribution of lesions on the hands (Courtesy of Dr Paul W Clough From Sutton and Sutton Diseases of the Skin)

Rabies

Synonyms—*Hydrophobia lyssa*

Definition—Rabies is a specific infection of canines and man It causes great excitability and mental derangement It is caused by a filtrable virus which is destroyed by drying heat and chemicals

Etiology—The virus may be passed from man to man through bites but man is most usually infected by the bite of a rabic dog and less often by a fox or wolf One of the earliest cases recorded in Canada is the death of General Simcoe Governor of Upper Canada from the bite of a wounded but rabic fox The virus is present in the saliva of a rabic animal The distribution of the disease throughout the world is quite irregular It is common in India France Spain Italy and other Mediterranean countries In Great Britain it is rare and in Australia it does not exist because of the strict canine quarantine in both countries In North America there are spotted foci of infection through many states In Canada there has always been an endemic area in central Ontario but until 1926 there had never been a recorded case east of Kingston Ontario In that year through lack of proper canine quarantine regulations it spread eastward through Ontario and Quebec but now appears to be again extinct

Symptoms and Signs—The virus is always introduced through the bite of a rabic animal which may have healed and been forgotten long before the initial symptoms appear Therefore the portal of entry may be indefinite The incubation period may vary from six weeks to six months or even a year This prolonged lapse of time is characteristic of the disease and during this period there are no symptoms The first indication is a soreness or numbness at the point where the bite was inflicted This is soon followed by dysphagia dyspnea and dysarthria These are due to a hypersensitiveness of normal reflexes This is soon followed by definite spasms particularly of the muscles of the pharynx larynx and diaphragm The slightest stimulus of sight sound smell or the desire to swallow may initiate a painful spasm It is from this last symptom initiated by the sight of water that the dehydrated individual suffers the most acute agony hence the synonym "hydrophobia or fear of water The spasms are intermittent and may cause a castanet like sound through the clicking of the teeth The voice is husky and the laryngeal spasms may eject a cry likened to a dog bark This stage is accompanied by fear mental excitation delusions hallucinations and even mania It lasts several days and is followed by a state of depression and exhaustion which soon progresses to coma and death

During the stage of excitation there is pyrexia due somewhat to toxemia but principally to the excessive muscular activity There is increased oxygen consumption sweating tachycardia thirst and finally vasomotor collapse with pallor Respiration may be sufficiently embarrassed to produce dyspnea and cyanosis All these symptoms are due to functional disturbances resulting from the spasms and closely resemble tetanus (see page 1341)

Pathological Anatomy—The pathological anatomy reveals in the ganglion cells of the cerebral and cerebellar cortex the typical and diagnostic

Negri bodies which are pathognomonic of the disease They are reddish masses with black dots within the cells There is a dispute as to whether these are the infecting organism or whether they are the result of cellular disintegration In addition the ganglion cells are degenerated and there are leucocytic infiltrations, and petechial hemorrhages in the brain and also throughout the viscera which are greatly engorged

Diagnosis—This is not difficult although it may at first be unsuspected if the history of a dog bite is not forthcoming It must be differentiated from tetanus, focal epilepsy, and hysteria Every vicious dog which bites a person should be put in quarantine until it is found rabic or not Its saliva may be injected into the brain of a rabbit which will promptly die of rabies If there is any doubt it should be killed and its brain examined for *Negri bodies* This is the only method of arriving at a definite diagnosis before it is too late to institute specific treatment

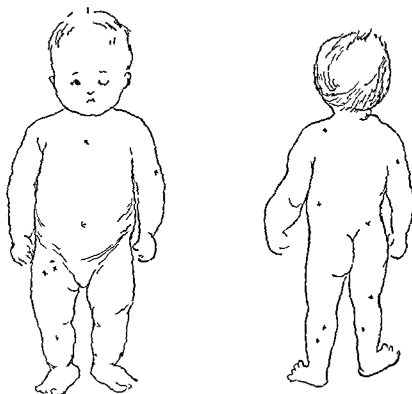


Fig 485—Distribution of rash in same case as Fig 486

Prognosis—Once the symptoms develop, death always occurs within a few days The earlier the specific vaccination is started the better the results

Treatment—The successful treatment of rabies depends entirely upon the recognition of the possibility of infection during the incubation period when the patient may be immunized so that when it is over, there is complete protection, which emphasizes the importance of ascertaining whether or not the dog or other canine that bites a person is rabic If this is not done, the possible diagnosis is purely speculative and unfortunately people are prone

to give the benefit of the doubt in favor of the animal s not being rabic or *kill the animal without being certain*

The vaccine is prepared by a number of methods They all depend upon some manner or other of attenuating the virus It is obtained from the brain and cord of an infected rabbit which is dried at a constant temperature over potassium hydroxide and then emulsified in salt solution In the original Pasteur vaccine it was preserved in 60 per cent of glycerine with about 0 5 per cent of tricresol In addition the following methods have been employed

Cummings—dialyzed against tap water
Hayes—different dilutions of a glycerine emulsion
Semple—1 per cent phenol emulsion
Harris—tissue dried in CO snow

Vaccines prepared by certain of these methods may be obtained from pharma ceutical firms or from public health departments with complete instructions as to their use which should be meticulously followed The course of treat ment usually extends over 14 to 19 daily injections each inoculation being properly numbered These preparations have done away with the necessity of the Pasteur Institute treatments of years ago There is no difficulty for any *physician carrying out this treatment*

Occasionally (1 in 5 000) cases so treated develop a peripheral paralysis There is no proved explanation for such and they are principally of aca demic interest

Rat-Bite Fever

Synonyms —Sodoku or sokosho Haverhill fever

Definition —*This is a specific infection following the bite of an infected* rat It has been reported as resulting from the bite of other rodents and also of a *cat Although it is common in Japan isolated cases are reported from* other countries both in Europe and America

Etiology —This disease may be caused by one of two organisms or both These are the *Spirillum minus* and the *Streptobacillus moniliformis* Although this disease is primarily a disease of wild rats it may be transmitted to man by other animals which have been bitten by infected rats such as the dog cat mouse and white laboratory rats As will be seen later it is important to differentiate which organism is responsible or whether both are This can to some degree be determined by the clinical course but best by the isola *tion from the patient of the specific agent*

Symptoms and Signs —After the rat bite there is an indefinite incuba tion period ranging from 5 to 21 days in the *spirillum type The bite wound is* usually healed The onset is sudden with pyrexia and often a chill There are headache malaise general muscular pains sweating and the other signs of a general infection The site of the bite becomes painful tender swollen and reddened (see Fig 486) There are surrounding edema and a spreading lymphangitis The tissues are often incised for nonexistent pus After a few days the pyrexia disappears and patient feels well There is a remission of *four to six days and another* paroxysm occurs which lasts about forty eight hours With each paroxysm an erythematous bluish red rash appears It

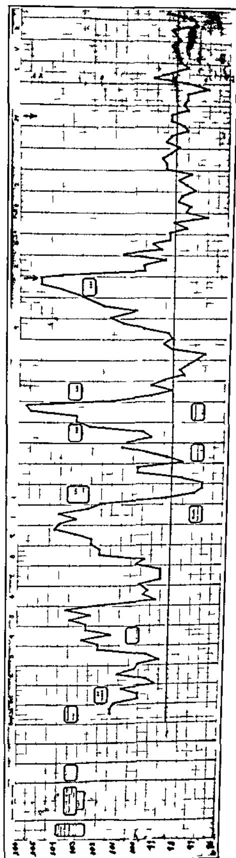


Chart XXXV.—Temperature chart in a case of rat bite fever



Fig. 480.—An illustration representing the acute exacerbation of the original local lesion in rat-bite fever.

is discrete papular and clear cut varying in size and is distributed over the trunk and limbs (see Fig 485) With each return of pyrexia the rash and the local disturbance about the bite wax and wane The neighboring glands are enlarged There is a leucocytosis with an eosinophilia and lymphopenia Severe anemia may eventually develop

In the streptobacillary form the incubation period is one to three days The bite heals promptly unless infected and does not show induration, inflammation or adenitis during the continuing course of the disease The relapses of pyrexia are not so regular

In both forms joint pains arthritis delirium and coma may appear It is interesting that a false positive Wassermann may occur in both forms but more commonly in the spirillar form as do also the severe toxic symptoms

Pathological Anatomy —The pathological anatomy shows but few changes The local lesion is a granuloma which does not suppurate unless secondarily infected while there are local necrosis and round celled infiltration This latter also occurs about the blood vessels in the rash

Diagnosis —The diagnosis is not at all difficult if the original bite is noted and the significance of the local recrudescence and rash are appreciated The recurring paroxysms suggest relapsing fever or malaria But there should be little confusion An absolute diagnosis can be made by finding the parasite in the blood stream but this is more difficult than would be expected This is best done in spirillar form by inoculating white mice or guinea pigs with the patient s blood exudate or tissue from the original lesion or lymph juice aspirated from the regional nodes The streptobacillus may be isolated by blood culture or lymph juice on special media Agglutinins to this bacillus may be found in the patient s serum as early as the tenth day

Course —The course in untreated cases may last for weeks or months Fulminating cases occur but are rare as are those without pyrexia Abortive cases which are unrecognized no doubt also occur Death results occasionally from exhaustion anemia emaciation and secondary infections The mortality was once stated to be about 10 per cent but this is much too high being more like 1 per cent

Treatment —This is specific The local lesion at the site of the bite should not be incised and arsenic in the form of arsphenamine or neoarsphenamine should be given in the usual doses (0 1 to 0 6 gm) in the spirillar type Usually two or three injections are sufficient but sometimes ten or more are required

Penicillin has been found to be most efficacious in both types In fact it will probably replace arsenicals entirely (see Chapter XX)

DISEASES CARRIED BY LICE, FLEAS TICKS AND OTHER BITING INSECTS

Lice fleas and ticks play an important role in the transmission of disease from animals to man These insects principally infect the rodent population of a community and spread the infection among these animals If such an infection reaches epidemic proportions increasing numbers of these in

sects harbor the infecting agent and therefore augment the possibility of its transmission to man, as they can transmit it not only from the lower animals to man but also from man to man It is after this manner that these epidemics begin and spread An example of such a transmission has already been mentioned in tularemia where in some *areas instead of man being infected* directly from the rabbit, the tick may act as a vector The virus is not inoculated into man by these insects but usually gain entrance by the excreta or crushed bodies of the insects being rubbed into abrasions or scratches

Most of the diseases carried by biting insects are caused by Rickettsia These are analogous to bacteria distributed amongst ticks mites, spiders, and insects There have now been identified three groups of human rickettsial diseases, namely (1) the typhus—louse and flea vector group, (2) the Rocky Mountain spotted fever—tick vector group, and (3) the tsutsugamushi—mite vector group

The first group comprise epidemic European type of typhus fever and the murine type which is endemic throughout the world and has its natural reservoir in the rat

The second group include Rocky Mountain spotted fever *São Paulo typhus of Brazil* (and other South American states), the *fievre boutonneuse* of the Mediterranean littoral *South African tick bite fever,* and *Kenya fever*

The third group consist of *tsutsugamushi disease of Japan (scrub typhus) rural typhus of Malaya,* and the *mite fever of Sumatra*

The principal Rickettsial diseases, their general geographical distribution, and vectors are found in Table XX

TABLE XX

DISEASE	GEOGRAPHICAL DISTRIBUTION	VECTOR
Typhus exanthematicus	Europe, Asia Minor Persia North China, Abyssinia North Africa Congo, Mexico	Louse *(Pediculus humanus)*
Endemic or typhus	World wide	Rat flea
Trench fever?	Western Europe North Africa	Louse *(Pediculus humanus)*
Rocky Mountin spotted fever (eastern and western types)	United States and Western Canada	*Dermacentor andersoni* *D variabilis*
South African tick typhus	South Africa, Kenya, Abyssinia	Ticks
São Paulo rural typhus	Southern Brazil and South America	Ticks
Q fever	Australia and United States	Ticks
Tsutsugamushi disease (scrub typhus)	Far East, India Malaya, Burma New Guinea, Formosa Japan, etc	Larval mite of *Trombicula akamushi* *T deliensis* *T fletcheri* *T walchi*
Carrion's disease	Narrow valleys of the Andes at altitudes of 2 000 to 9 000 feet in Peru Ecuador Chili Bolivia and Colombia	Sand fly *(Phlebotomus noguchi* and *P verrucarum)*

Typhus Fever

Synonyms—Brill s disease jail fever camp fever, ship fever, Fleck typhus Fleckfieber tabardillo typhus exanthematicus, spotted fever

Definition—Typhus fever is a specific infectious disease characterized by an abrupt onset, a purpuric eruption great prostration and a crisis about the tenth to fourteenth day It is conveyed by lice and fleas There is every reason to believe that for generations many diseases passed in the disguise of this infection as the many popular names indicate and its rough similarity to relapsing fever, typhoid fever trench fever epidemic meningitis and Rocky Mountain spotted fever to which the synonym of spotted fever" should alone be applied



Fig 48 —Photograph showing the rash in typhus (Courtesy of Dr J L Todd)

Etiology—In 1909 Nicolle demonstrated that the cause of European typhus fever was transmitted from person to person by lice Since then great advances have been made in the control of this disease especially through the knowledge of the fact that the American variety is also conveyed by the rat flea which not only conveys it from rat to rat but also from the rat to man The disease is caused by the *Rickettsia prowazeki*—almost simultaneously described by Ricketts and Prowazek These Rickettsia are minute (1 to 1 5 microns long) gram negative rod shaped bodies They often appear in coccoid form particularly in the feces of the louse or flea They are deposited on the skin by these parasites and are rubbed into the skin through the punctures made by them or abrasions caused by scratching The evidence favoring Rickettsia as the cause of typhus fever is overwhelming The constant association of the *Rickettsia prowazeki* whether in lice guinea pigs other laboratory animals and men as well as the specific immunological studies and tissue cultures all weave a web of proof that is practically incontro

sects harbor the infecting agent and therefore augment the possibility of its transmission to man, as they can transmit it not only from the lower animals to man, but also from man to man. It is after this manner that these epidemics begin and spread. An example of such a transmission has already been mentioned in tularemia where in some areas instead of man being infected directly from the rabbit, the tick may act as a vector. The virus is not inoculated into man by these insects but usually gain entrance by the excreta or crushed bodies of the insects being rubbed into abrasions or scratches.

Most of the diseases carried by biting insects are caused by Rickettsia. These are analogous to bacteria distributed amongst ticks, mites spiders, and insects. There have now been identified three groups of human rickettsial diseases namely (1) the typhus—louse and flea vector group, (2) the Rocky Mountain spotted fever—tick vector group, and (3) the tsutsugamushi—mite vector group.

The first group comprise epidemic European type of typhus fever and the murine type which is endemic throughout the world and has its natural reservoir in the rat.

The second group include Rocky Mountain spotted fever, *Sao Paulo typhus of Brazil* (and other South American states) the *fièvre boutonneuse* of the Mediterranean littoral, *South African tick bite fever* and *Kenya fever*.

The third group consist of *tsutsugamushi disease of Japan (scrub typhus)*, *rural typhus of Malaya*, and the *mite fever of Sumatra*.

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Carrión's disease	Narrow valleys of the Andes at altitudes of 2 000 to 9 000 feet in Peru Ecuador Chili, Bolivia and Colombia	Sand fly *(Phlebotomus noguchi* and *P verrucarum)*

severity of the disease is influenced by the previous state and nutrition of the patient, *the older the patient, the more serious the course and the higher the* mortality In childhood the disease is mild and death rarely occurs in those under twenty Sex has no influence

The principal complications are bronchitis and bronchopneumonia which in some epidemics account for much of the mortality Other secondary infections in the salivary glands and middle ear sometimes occur But in addition to the pulmonary lesions the most serious complications are due to arterial thromboses both visceral and cutaneous This may occur in the mesenteric renal splenic carotid pulmonary or any artery with organismal necrosis Thromboses of the arteries in the skin and subcutaneous tissue account for the large area of superficial necrosis and gangrene (see Fig 488) Bed sores and symmetrical gangrene also occur The relation *to thromboangiitis* obliterans has been referred to (see page 466)

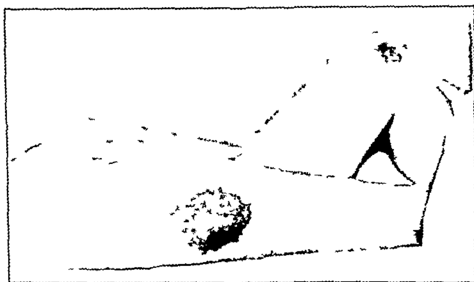


Fig 488 —Photograph showing the rash in typhus with areas of purpura and gangrene (Courtesy of Dr J L Todd)

The mortality varies considerably in different epidemics from as low as 5 per cent to 70 per cent In the mild endemic form in America it is probably about 3 per cent while in the severe outbreaks in Eastern Europe and Russia it was devastating

Diagnosis —*The early diagnosis before the appearance of the rash is* difficult as the symptoms are like those of any acute infection which begins suddenly Malaria relapsing fever pneumonia epidemic meningitis smallpox scarlet fever measles rat bite fever Rocky Mountain spotted fever etc may have to be differentiated but this is not difficult as a rule once the rash has appeared *except in those with a purpuric eruption*

The Weil Felix agglutination reaction is constant after the appearance of the rash This is performed with a standard culture of *B proteus* which has been distributed to most bacteriological laboratories *in the world* The test is done with either living or dead emulsions by the microscopic or macroscopic

vertible There are also strong indications that the virus may remain dormant for many years, and this may explain the sporadic case in which neither lice nor fleas can account for the transmission of the disease when there is no source of the infection in the rest of the population

Symptoms and Signs —The incubation period is from eight to twelve days, although in mild infections it may be longer Toward the end of this time, the patient may have vague malaise and headache and even a slight pyrexia But the real onset of the disease is sudden, with a chill, rigor, and high fever There are considerable prostration and general pains The alertness and mental excitation with flushed face and injected conjunctivae are striking features Early delirium is common The spleen is palpable, and anorexia and vomiting sometimes are present

Between the third and the seventh day, usually on the fifth, a macular irregular erythematous eruption appears over the neck, thorax abdomen, and extremities There may also be a diffuse erythema which makes the maculae less obvious as these are not as a rule palpable, although sometimes they may assume large size and be felt As the erythema fades, they become more apparent The degree of the eruption is roughly proportionate to the severity of the disease From a pink it gradually changes to a deeper pink then purplish and finally brownish color due to perivascular extravasations In severe cases the rash is purpuric and there are then hematuria, hematemesis and melena

The other manifestations are bronchial rales, cough and sputum due to a bronchitis which may extend to the bronchioles and cause a bronchopneumonia which is insidious in onset and is no way different from this lesion occurring in other diseases There may also be present streptococcal or pneumococcal infections which may accordingly modify the pulmonary lesions The pulse is always rapid, the blood pressure low, and signs of cardiovascular collapse are common in the severe cases There is a moderate leucocytosis as a rule, with occasional high count which is an unfavorable sign Intense delirium and nervous symptoms may closely simulate meningitis They are more prevalent in typhus fever than any other acute infectious disease The *endemic* or *murine typhus* is similar to the epidemic form except that it has a less severe symptomatology The rash is less intense and extensive petechiae and purpura are less common and necrosis does not occur

Pathological Anatomy —The pathological anatomy of typhus fever is microscopic rather than macroscopic The spleen is large and soft but the chief characteristics are the "typhus nodules" of Fraenkel, which are perivascular infiltrations about the small vessels of the skin leading to thromboses and sometimes necrosis Similar proliferative lesions occur about the small arteries, veins, and precapillaries including the central nervous system where they are particularly abundant and undoubtedly account for the intensity of the mental symptoms Thromboses in the larger arteries and veins are not uncommon and account for the most serious of the complications

Course —The course of this disease is usually from ten to fifteen days, when in favorable cases the temperature falls by crisis or rapid lysis The

by an ulcer with a yellowish base This primary lesion may be situated almost any place on the body except for the palms soles and scalp It should be carefully looked for About the end of the first week a nonhemorrhagic macular or maculopapular rash appears on the trunk and may spread to the limbs

The leucocyte count slowly rises to about 15 000 cells per cu mm but may be higher if complications develop The Weil Felix reaction usually becomes positive during the second week but its absence should not exclude this disease

The *complications* are most apt to develop during the second week and comprise pneumonia encephalitis and circulatory collapse which vary greatly in intensity

Diagnosis —The diagnosis depends largely upon the finding of the *eschar* and the general clinical pattern Although the Weil Felix reaction occurs late it should be repeatedly tested for to confirm the final diagnosis This disease should be differentiated from common diseases in the area such as malaria infectious hepatitis and dengue

Prognosis —The mortality in different localities would seem to suggest a variable virulence of different strains of *R orientalis* Other factors may be operative such as general nutrition and the presence of chronic diseases such as dysentery malaria and age It varies from 1 to 60 per cent The presence and severity of pneumonia is often the determining factor Therefore although death may occur in the second week it is usually delayed until the third

Treatment —Prevention depends upon avoidance of the vector If this cannot be assured then the clothing should be systematically impregnated with a mite repellent such as dimethyl or methyl phthalate or benzyl benzoate

As there is no specific cure for this disease the patient should be treated on those general lines appropriate to any acute infection such as bed rest adequate caloric water and salt intake (the environment temperature and humidity being taken into account) and hydrotherapy Oxygen should be given continuously in pneumonia with cyanosis

Penicillin and the sulfonamides should be avoided unless there is a secondary infection (pneumonia) due to an organism which is sensitive to them Recent reports suggest that para aminobenzoic acid may be effective as a chemotherapeutic agent

Trench Fever

Synonyms —Shin fever shank fever Meuse fever Russian intermittent fever Volhynian fever five day fever Polish fever gaiterpain fever His Werner disease

Definition —Trench fever is a prolonged recurring infectious disease with severe pains in the shins prostration splenomegaly and a rosy macular rash

Etiology —This disease is probably caused by a Rickettsia (*R wolhynica R pediculi R quintana*) which is transmitted from man to man by the body louse Therefore it often occurs in epidemics in overcrowded and unclean districts It has not been described in civilian life but enormous numbers

agglutination technic A positive reaction, agglutination of 1 50 or higher, appears about the fourth day and reaches its maximum just before the crisis It is specific except that it also is positive in Rocky Mountain spotted fever and tsutsugamushi disease (see below) The only certain method of differentiating these two is based upon the fact that guinea pigs which have recovered from typhus fever are immune but not to spotted fever, and vice versa

Treatment—*Prophylaxis* is principally the extermination of lice and fleas, in other words delousing the whole population All personal clothing, bed clothes and mattresses should be sterilized Delousing of all bedding and clothes has been rendered much simpler by the generous use of DDT (dichloro diphenyl trichloro ethane) Attendants should be protected from contamination by these insects by wearing louse proof clothing, and in addition the head must be covered and rubber gloves worn In epidemics especially all attendants should be careful not to transport these parasites on their clothes Most successful results have been obtained by protective vaccination and there is hope that a curative serum may soon be available

The *active treatment* is symptomatic as there is no specific remedy A sufficient caloric diet should be assured and dehydration must be prevented by copious fluid intake Pyrexia is controlled by external hydrotherapy and an ice bag constantly applied to the head is often beneficial for headache and delirium In fact it is the same as for all acute febrile diseases Particular attention should be directed to the prevention of bed sores and superficial gangrene which so easily develop This is best done by careful protection to pressure points by air cushions and rings

Tsutsugamushi Disease

Synonyms—Scrub typhus tropical typhus rural typhus Japanese river fever mite borne typhus kedani disease

Definition—Tsutsugamushi disease is an acute specific rickettsial disease conveyed to man by a mite The disease is chiefly characterized by a primary lesion at the site of the attachment of the mite and a macular rash

Etiology—This disease is caused by *R orientalis* (sometimes called *R tsutsugamushi* and *R nipponica*) which is transmitted to man by the larval form of several mites of the genus Trombicula Of the many species of these mites, it would seem that only four are responsible namely *T akamushi T deliensis, T fletcheri*, and *T walchi* The animal reservoir are certain field rodents

Symptoms and Signs—The incubation period is ten to eighteen days and the onset is sudden with headache chilliness and fever which rises gradually reaching a maximum of 102° to 105° F during the second week continues into the third week and then falls by lysis The signs of general intoxication are increasing headache anorexia lethargy and sometimes a low delirium The more local signs are conjunctivitis deafness regional lymphadenitis and brachycardia

The area where the tick has been implanted is often the site of an *eschar* which represents the primary lesion This may be a roundish ulcer averaging 5 to 7 mm in diameter covered with a dark crust and surrounded by a pinkish elevated zone In some areas the crust may not be present but is replaced

by an ulcer with a yellowish base This primary lesion may be situated almost any place on the body except for the palms soles and scalp It should be carefully looked for About the end of the first week a nonhemorrhagic macular or maculopapular rash appears on the trunk and may spread to the limbs

The leucocyte count slowly rises to about 15 000 cells per cu mm but may be higher if complications develop The Weil Felix reaction usually becomes positive during the second week but its absence should not exclude this disease

The *complications* are most apt to develop during the second week and comprise *pneumonia encephalitis, and circulatory* collapse which vary greatly in intensity

Diagnosis —The diagnosis depends largely upon the finding of the *eschar* and the general clinical pattern Although the Weil Felix reaction occurs late it should be repeatedly tested for to confirm the final diagnosis This disease should be differentiated from common diseases in the area such as malaria infectious hepatitis and dengue

Prognosis —The mortality in different localities would seem to suggest a variable virulence of different strains of *R orientalis* Other factors may be operative such as general nutrition and the presence of chronic diseases such as dysentery malaria and age It varies from 1 to 60 per cent The presence and severity of pneumonia is often the determining factor There fore although death may occur in the second week it is usually delayed until the third

Treatment —Prevention depends upon avoidance of the vector If this cannot be assured then the clothing should be systematically impregnated with a mite repellent such as dimethyl or methyl phthalate or benzyl benzoate

As there is no specific cure for this disease the patient should be treated on those general lines appropriate to any acute infection such as bed rest adequate caloric water and salt intake (the environment temperature and humidity being taken into account) and hydrotherapy Oxygen should be given continuously in pneumonia with cyanosis

Penicillin and the sulfonamides should be avoided unless there is a secondary infection (pneumonia) due to an organism which is sensitive to them Recent reports suggest that para aminobenzoic acid may be effective as a chemotherapeutic agent

Trench Fever

Synonyms —*Shin fever shank fever Meuse fever Russian intermittent* fever Volhynian fever five day fever Polish fever gaiterpain fever His Werner disease

Definition —Trench fever is a prolonged recurring infectious disease with severe pains in the shins prostration splenomegaly and a rosy macular rash

Etiology —This disease is probably caused by a Rickettsia (*R wolhynica R pediculi R quintana*) which is transmitted from man to man by the body louse Therefore it often occurs in epidemics in overcrowded and unclean districts It has not been described in civilian life but enormous numbers

of soldiers were infected during World War I and a lesser number during World War II, hence the name "trench fever" and most of its synonyms The Rickettsia has been found in the blood, urine and tissues of those infected It is supposed to gain entrance through the skin by the excreta or dead bodies of the louse being rubbed into the skin through scratches or other abrasions

Symptoms and Signs.—The incubation period is uncertain but is probably somewhere between fourteen to twenty eight days The onset is sudden with a chill and pyrexia up to 102° F or 103° F, and tachycardia This may be preceded by a short period of general malaise, headache, and muscular pains But with the real onset, prostration, muscle and bone pains chiefly in the legs, and anorexia, become prominent symptoms In addition there is splenomegaly and a fairly characteristic rash upon the chest and abdomen It closely resembles the rose spots of typhoid fever It consists of discrete red papules measuring a few millimeters to a centimeter in diameter They disappear on pressure

These symptoms and signs are not exclusively characteristic of trench fever but may simulate and be simulated by other infectious diseases except that the pains in the legs are conspicuously severe The pyrexia is, however, of special importance in that it runs through recurring remissions and exacerbations, and with each there is a waning and a waxing of all the signs and symptoms including the rash This periodicity is irregular, and recrudescences or relapses may recur after months or even years It has also been demonstrated that the virus may remain viable for many months and lice may be infected from patients over a year after the onset of the disease

There are, in addition to these symptoms and signs a mild bronchitis, and in the early stages moderate leucocytosis (12 000 per cu mm) but this fluctuates considerably and a leucopenia is often found Anorexia with vomiting has also been reported

Pathological Anatomy.—This is not known as the disease is not fatal and therefore there has been no opportunity to make a complete examination The only tissue which has been examined is the skin Biopsy reveals the rash to be due to a lymphocytic perivascular infiltration with a few polymorphonuclear cells Local necrosis does not occur

Diagnosis.—This as a rule, is comparatively easy when it occurs among troops or in other crowded and unsanitary areas Sporadic cases are usually overlooked unless the patient suggests it himself from past experience It is usually confused with influenza typhoid fever paratyphoid fever rheumatic fever, relapsing fever malaria, dengue and typhus fever There is no specific test either by immunological or bacteriological diagnostic methods The diagnosis must therefore rest upon clinical evidence

Prognosis.—The course of the disease is prolonged and relapses after prolonged periods are not uncommon but death does not occur The disease however, leaves a chronic debility which may last for years and it would seem that the virus remains viable in man for a long time and may be the cause of these chronic and persistent disabilities

Treatment.—The treatment of trench fever is entirely symptomatic and such as is employed in all acute infections Antipyretics analgesics and

hydrotherapy are indicated in the management of the pains and pyrexia The convalescence is prolonged and the patient must be guarded against too hasty return to active life This is particularly so in soldiers who should be slowly and gradually reconditioned for strenuous training because physical signs are not detectable to contraindicate it although the symptoms of dyspnea tachycardia and precordial pain on exertion sweating and easy fatigue are significant of a continuing "debility" D A H irritable heart or neurocirculatory asthenia all synonyms of the same syndrome (page 373)

The other Rickettsial diseases shown in Table XX present a clinical pattern similar to that of typhus although in general much less severe In scrub typhus the bite of the larval mite may result in an ulcer with lymphangitis and adenitis The rash usually commences on the face and does not become petechial The death rate in these allied conditions is low and there is no known specific therapy Symptomatic treatment for infectious diseases is indicated

Rocky Mountain Spotted Fever

Synonyms —Tick fever black fever

Definition —Rocky Mountain spotted fever is an acute specific disease caused by a Rickettsia called *Dermacentroxenus* and is conveyed to man by the wood tick The disease is chiefly characterized by a macular eruption which becomes purpuric

Etiology —This disease was first found in the western states of North America but it has spread to the western provinces of Canada and farther afield where the wood tick or *Dermacentor andersoni (venustus)* abounds This is the sole method of transmission of the virus which is a Rickettsia named by Wolbach the *Dermacentroxenus rickettsi* It is similar to the *Rickettsia prowazeki* except that it invades and grows in the nuclei of cells whereas the latter *remains in the cytoplasm This virus is transmitted from one generation* of ticks to another and man is not a necessary intermediate host The disease can be readily duplicated in the monkey rabbit and guinea pig

Symptoms and Signs —The incubation period is from four to eight days and the portal of entry is through the skin There may be slight prodromal symptoms such as malaise anorexia and chilliness but the real onset is sudden with a chill and pyrexia There are severe muscle bone and joint pains particularly in the back and legs with intense headache The face and conjunctivae are injected and there is photophobia The body temperature is high usually between 104 F and 105 F although it has been reported as high as 107° F It reaches its maximum during the second week There are a tachycardia and tachypnea in excess of that expected with the pyrexia the pulse is small and weak and the respirations are shallow

On the third to fifth day of the disease a rash appears first upon the wrists ankles and back and extends over the arms legs chest abdomen and forehead It may also appear on the mucous membranes of the mouth and pharynx It is a rosy macular eruption (2 to 5 mm) not palpable and disappearing on pressure at first but after a few days it changes to a purpuric or petechial character and at this time cutaneous and subcutaneous hemorrhages

may develop As the days pass, the rash becomes more extensive and tends to be confluent in the more severe cases In the milder ones it remains discrete and produces a mottled appearance Thrombosis of the cutaneous vessels causes the skin to assume a dark purplish to bluish color in areas where the skin is delicate There may also be necrotic areas in the skin of the fingers, toes, ears, scrotum, prepuce, vulva, and the mucous membrane of the uvula and soft palate Insomnia, restlessness, delirium and hyperesthesia are distressing symptoms In the most severe cases convulsions, hypertonia, even to opisthotonos, and coma may occur

The spleen is enlarged and palpable, and there is usually a slight leucocytosis rarely above 12 000 per cu mm Anemia occurs but the erythrocytes seldom number less than 3 000 000

Pathological Anatomy—The essential lesion in this disease is found in the blood vessels where there is an endangiitis leading to thrombosis which is accountable for the hemorrhagic and necrotic lesions of the skin Hemorrhages also occur in the testicle and ovary but not in the other viscera Microscopically there is proliferation of the endothelium and surrounding the vessels there is a good deal of infiltration and the Rickettsia are found in the endothelial and medial cells Pneumonia is the principal visceral lesion but even this is not common



Fig 489—Rocky Mountain fever showing characteristic eruption (Courtesy of Dr John J Sippy From Sutton and Sutton Diseases of the Skin)

Diagnosis—The close similarity of this disease to typhus fever makes its differentiation obviously important (see page 1353) Other diseases which it may resemble are typhoid fever cerebrospinal fever, and measles The rose spots of typhoid fever are palpable while the slow onset leucopenia Widal reaction and positive blood culture soon clarify the diagnosis In the early stages the rash may closely imitate that of measles and although there is no coryza, the photophobia may lead to confusion but the absence of Koplik's spots and lymphadenopathy and the distribution of the rash makes the distinction of these diseases comparatively easy However when a case of Rocky Mountain fever is first seen in the second week and there are pronounced nervous symptoms it may be difficult to distinguish it from meningococcal meningitis A lumbar puncture will give positive evidence

Course and Prognosis—The disease usually runs its course in three weeks and the pyrexia terminates by lysis with this there is a rapid improvement,

and if the rash has been pronounced, desquamation occurs The severity of *the case is not in proportion* to the intensity of the rash, but rather is directly indicated by the tachycardia and tachypnea Death usually occurs between the eleventh and seventeenth days The mortality rate varies greatly in different regions from about 4 per cent in Idaho to nearly 90 per cent in the Beet Root valley of Montana while in the eastern portion of the same state it is about 15 per cent In children the mortality is quite low but increases with each decade

Treatment—*Prophylaxis*—As the disease is conveyed by the wood tick it occurs in areas and during the period of the year (March to June inclusive) when this insect is active Therefore the control of the disease is the extermination when possible of the vector This is best done by destroying small animals which harbor the larvae, and by dipping cattle so infested The cultivation of land usually eradicates the source but it continues in waste spaces and on the range A protective vaccine is now available and its value has definitely been demonstrated in that it protects against less virulent strains and lessens the severity of the more virulent

Specific—Treatment of individual cases is upon symptomatic lines as there are no proved specific measures although a rabbit anti serum has been produced which seems encouraging as is para amino benzoic acid Many drugs have been used without benefit A nutritious diet hydrotherapy and plenty of fluids as in all infectious diseases, with good nursing are the best methods of procedure The restlessness and hyperesthesia require sedatives and at times morphia as they aggravate the exhaustion which is inherent in all severe infections

Relapsing Fever

Synonyms—*European relapsing fever spirillosis febris recurrens famine* fever

Definition—It is an acute infectious disease with recurrent periods of *pyrexia and afebrile intervals both of which are of six to seven days* duration It is caused by the *Spirillum recurrentis* or Obermeier's spirillum It occurs in many countries but the spirillum is not always the same In Europe it is caused by a variant called the *Spiroschandmmia recurrentis*, in North America by the *Spirillum novyi* in Africa by the *Spirillum duttoni* and in Asia by the *Spirillum carteri*

Etiology—The spirillum is carried by lice and certain ticks of the genus *Ornithodoros* and these vectors are naturally most prevalent under conditions of filth poverty and famine The infection is commoner in women and in young adults

Symptoms and Signs—There is a short incubation period of about six days during which there is general malaise and muscle pains The onset of the paroxysm is explosive with a chill and acute pyrexia There are also the usual symptoms of an acute infection such as headache general malaise with pains in the back limbs and joints with sometimes nausea and vomiting The body temperature may reach 105 F to 107° F with a proportionate tachycardia of 140 to 160 per minute The spleen is *enlarged and palpable* A

lower pyrexia continues for six or seven days and then there is a crisis to be followed after a like period by another paroxysm

In addition to these febrile cycles there may appear during the pyrexia cough, laryngitis glossitis, parotitis, cervical adenitis, arthritis, orchitis, and edema of the feet Skin eruptions are common, particularly in the severe cases, such as purpura urticaria, herpes, scarlatinal and morbilliform rashes while in the most severe cases hematemesis, hemoptysis, melena and hematuria may accompany the purpura, all indicating a severe toxic permeability of the capillaries As the paroxysm reaches a termination, diarrhea and sweating indicate the impending crisis There is a polymorphonuclear leucocytosis and the parasite is readily found

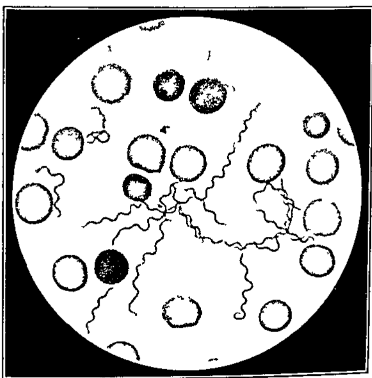


Fig 490 —Photomicrograph showing *Spirocheta duttoni* in the circulating blood (Courtesy of Dr J L Todd)

Pathological Anatomy—The pathological anatomy is in no way specific, revealing only an enlarged and septic spleen and cloudy swelling with cellular degeneration no different from any other intense infection

Diagnosis—This disease in the original paroxysm must be differentiated from influenza pneumonia malaria typhus fever and dengue fever The direct diagnosis is arrived at by finding the parasites in the circulatory blood This is done by examining a fresh specimen either by direct or oblique rays A dried smear stained by a polychrome method will also reveal them

Prognosis—The course is confined to the first paroxysm in a third of the cases In the others there may be two or more Most recover from the first but each succeeding paroxysm takes its toll through exhaustion and toxemia particularly in the elderly and those reduced by poverty and starvation The

mortality has varied from one to six per cent in epidemics and this difference depended upon the economic status of the population at the time

Treatment is specific with arsenicals The spirochetes disappear from the blood and the temperature returns to normal after neoarsphenamine (0 01

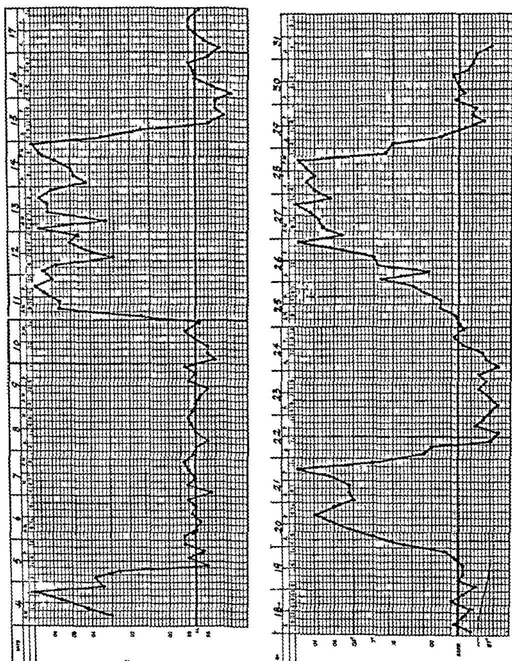


Chart XXXVI —Temperature chart in a case of relapsing fever

gm per kilogram of body weight) or mapharsen (0 045 gm) intravenously or stovarsol (0 25 gm for 6 doses daily) by mouth These should be given at the beginning of a paroxysm of fever and not toward the crisis Penicillin

has also been used with success in a small number of cases (see Chapter XX) If there is a relapse, a repeat dose is usually sufficient to terminate the infection During convalescence it is important to remain at rest for a week to ten days to avoid recurrences The ordinary symptomatic treatment of all infections should be followed It is palliative but in no way curative

Plague

Definition—Plague is an acute specific infectious disease caused by the *Pasteurella pestis* which is usually conveyed to man by fleas from the rat or other rodents There are two main types—the *bubonic* in which lymphadenopathy is the principal sign and the *pneumonic* where there is diffuse pneumonia

Etiology—The *Past pestis* is a bipolar staining, gram negative bacillus which grows readily on ordinary culture media It infects rats, ground squirrels guinea pigs and other small rodents, and the camel The bacillus may be carried by bedbugs and flies, and in this manner man may occasionally be infected The principal flea which transmits the disease in the *Xenopsylla cheopis* or rat flea This parasite conveys the organism from rodent to rodent and thence to man In certain areas the particular rodent population is always infected to some extent but before an epidemic this incidence rises rapidly and is foretold by their greatly increased death rate The pneumonic form is transmitted by droplet infection as the sputum contains enormous numbers of the bacilli All classes ages, and both sexes are susceptible, but it occurs most commonly among those exposed to fleas Therefore personal cleanliness is of first importance in escaping infection

Symptoms and Signs—The incubation period is two to seven days, and as already mentioned the portal of entry is through the skin or by inhalation of infected droplets of sputum The onset is sudden with a chill and pyrexia ranging from 102° F to 105° F There are violent headache vertigo, and great prostration The face and conjunctivae are injected, but the whole expression is one of great weariness which is characteristic of the disease There are pronounced tachycardia and tachypnea The tongue is swollen and much furred, while there may be vomiting at the onset and diarrhea sometimes occurs The spleen and liver are palpable and there is a polymorphonuclear leucocytosis

In the bubonic form within twenty four hours the lymph glands become painful and rapidly enlarge especially those in groin, axilla and neck The first are usually the most prominent They sometimes suppurate The mesenteric glands may also be involved and this causes abdominal tenderness In a few cases the infection seems to gain entrance through the throat, and the glands of the neck are most prominent

In the pneumonic form the general features are similar but there are cough with hemorrhagic and watery sputum which contains enormous numbers of the bacilli Signs of bronchopneumonia soon develop and the patches coalesce to form massive areas of consolidation The incubation period is shorter than in the bubonic type It should not be confused with a secondary pneumonia

There is also recognized a *septicemic form* in which there is an overwhelming blood infection The patient usually dies before either the buboes or pneu

monia can develop Quite the opposite to this type is a mild form called *pestis minor* or *ambulatory plague* All the symptoms are of slight degree, although the buboes may suppurate The patient frequently continues to be up and about and is a source of danger in spreading the disease, as it is just as infectious as the severer forms

In the severe cases there may be petechiae, ecchymoses and hemorrhages from the skin, mucous membranes and kidneys Occasionally vesicular or pustular eruption occurs, and there may be cutaneous necrosis

Pathological Anatomy—*The portal of entry on the skin may sometimes* be recognized by a small vesicle The lymph glands show intense congestion and hemorrhagic edema Those draining the portal of entry are most severely involved and in the surrounding tissues there is also edema and hemorrhage There is widespread injury to the vascular endothelium which is productive of hemorrhages into the skin mucous membranes spleen kidneys, meninges and brain There may also be intense congestion of the respiratory and gastro intestinal tract In the septicemic form although the lymph glands are not grossly affected, on microscopical examination there are found hemorrhagic extravasations In the pneumonic form there is an intense inflammatory reac *tion in the bronchial mucous membrane which extends into the peribronchial* and bronchiolar tissues and alveoli The bronchial and tracheal lymph glands are enlarged although the others may not be

Diagnosis—Plague may be confused with influenzal pneumonia in the pneumonic type or with tularemia, syphilis and acute mononucleosis in the bubonic form Bacteriological examination of the sputum establishes the diagnosis in the first, but in the mild forms of the bubonic variety the diag nosis may be more difficult It should always be suspected in areas where plague has ever been and especially in seaports Absolute proof can be ob tained by gland puncture or biopsy and inoculating proper laboratory animals or culture media *with the gland juice The organisms may be recognized in* smears from such, but a negative result is not conclusive In the septicemic cases they may be found in blood smears and blood cultures are always positive and frequently so in other forms

Course and Prognosis—The duration of the *disease in those that recover* is usually about four to eight days and if a case lasts a week it usually re sults in recovery The pneumonic and septicemic cases nearly all end in death within a few days although mild cases of the latter may end in recovery In bubonic plague the mortality varies in different epidemics from 30 to 90 per cent Infants and children are less severely affected than adults With re covery there is a certain degree of immunity which may protect from a second attack or render it quite mild

Treatment—*Prophylaxis* rests to a great extent upon the suppression of the rodent population in infected areas, and the prevention of their transpor tation by sea Individual protection depends upon thorough personal clean liness wearing rubber gloves when handling infected material and a face mask when attending or nursing pneumonic cases Antiplague vaccine has been extensively used and appears *to produce a moderate immunity for a short* indefinite period but will not protect against a massive infection

The treatment of the individual is the same as that for any acute infection. Hyperpyrexia must be controlled with hydrotherapy. In addition, sulfadiazine should be given in full doses (see Chapter XX). High blood levels should be attained (20 mg. per cent) and continued over four to five days and then the amounts should be gradually reduced but continued after the temperature reaches normal. If necessary, it should be given intravenously. This is advisable in severe cases and when the therapy is started late in the disease.

Q Fever

Definition.—Q fever is an acute febrile disease which has been identified in the Southwest of the United States and in Australia.

Etiology.—It was at one time thought to be due to two separate rickettsiae, namely, *burneti* in Australia and *diaporica* in the United States, which are now believed to be identical. It has not been definitely proved that the vector is the tick, although the organism has been isolated from them. It has occurred in forest workers, slaughter and packing house employees and train crews in cattle trains. The animals which are most likely to carry the vector are cattle, pigs and bandicoots (Australia).

Symptoms and Signs.—The onset is sudden with pyrexia, sometimes chills, nausea, vomiting, headache and a leucocytosis. General pain in the limbs may be prominent with some stiffness of the neck, severe sweats and insomnia. There is sometimes cough, which is usually unproductive but may on occasion be accompanied by a small amount of thick, tenacious mucoid sputum, rarely blood tinged. Thoracic pain of a neuralgic rather than pleural type may be present. The physical signs are few or absent except over the lungs where rarely a scattered distribution of rales and changed breath sounds are heard but x-rays commonly reveal a patchy infiltration similar to broncho- or atypical pneumonia.

Diagnosis.—The diagnosis is usually made by recognizing the possibility of such an infection and demonstrating agglutinins to the rickettsia in the blood. The Weil-Felix reaction with proteus bacilli is negative.

Prognosis.—The disease may last for one to two weeks. The mortality varies in different outbreaks from 1 to 5 per cent.

Treatment is symptomatic.

Bullis Fever

Synonyms.—Lone Star fever. Texas tick fever.

An acute febrile disease broke out in those who had been the victims of many tick bites in the Bullis camp area in Texas. The onset was sudden with chills and pyrexia of 102° to 104° F. The principal symptoms were prostration, anorexia, weakness and weight loss, while the signs included a maculopapular rash on the trunk, lymphadenopathy and a leucopenia. The blood cultures were always negative as were serum reactions. There is still some controversy as to whether this disease is caused by a virus or a rickettsia.

The duration of the disease is 4 to 14 days and the death rate almost nil. The **treatment** is symptomatic.

Colorado Tick Fever

The Colorado tick fever is a milder febrile disease closely resembling the Texas type It is transmitted by tick bites and exhibits general myalgia photophobia leucopenia negative Weil Felix reaction and a definite remittent interval The cause has not been identified although the tick bite may develop into an indolent ulcer

The **prognosis** is good and the **treatment** symptomatic

Rickettsialpox

In 1946 a fairly localized outbreak of an unclassified acute infectious disease was reported by the New York City Health Department

The onset occurred with a primary papular lesion This was roundish and firm without surrounding erythema It gradually grew in size developed a central vesicle which was deep and firm The lesion eventually became a black eschar

About one week after the start of the initial lesion there was a sudden onset of chills fever backache sweats and prostration At this time a discrete maculopapular erythematous rash developed In a few days a vesicle appeared which shortly dried leaving a black crust There was usually a leucopenia The Weil Felix reaction was negative Rickettsial strains were isolated from the blood of several patients and from pooled blood of rodent mites *Allodermanyssus sanguineus*

The disease ran a comparatively mild course There were no deaths and the treatment was symptomatic

Swineherd s Disease

Synonyms—Maladie de Bouchet pseudotyphoid meningitis

Definition—Bouchet in 1914 described in Haut Savoie an acute febrile disease conveyed apparently from swine to man characterized by a preliminary typhoidal phase of headache malaise skeletal pains and abdominal symptoms A period of remission is followed by a second phase with meningeal symptoms

Etiology—*Bacteriological examinations of the blood have been negative* but the virus is uniformly in the blood and passes through an L candle The urine is likewise infective in a large percentage of cases while the cerebrospinal fluid is less frequently so It has been transferred from man to man through twenty one passages by plasma inoculation but apparently does not occur by case to case infection The serum of convalescent patients neutralizes the virus The manner of its conveyance from pigs to man is unknown but the louse is suspected There is strong evidence that it is due to a filterable virus The disease is supposed to affect young pigs one to two months of age sometimes in epidemic form producing convulsions It lasts about fourteen days and has a low mortality

Incubation Period—The incubation period is about twelve days in the experimental disease

Onset and Course—The onset is fairly acute with pyrexia headache muscle pains and prostration soon followed by vomiting diarrhea and meteorism

and occasionally melena This preliminary state lasts about four days when there is a remission to be followed in about forty eight hours by a second rise of temperature and signs of meningeal irritation This phase is not constant Conjunctivitis is common as is a nonhemorrhagic macular or maculopapular rash on the abdomen and inner aspects of the thighs just before the remission There is a polymorphonuclear leucocytosis In the second phase the cerebro spinal fluid is under pressure and several hundred lymphocytes per cubic millimeter are present

The disease terminates in a crisis or rapid lysis in about nine days and is very seldom fatal

The **treatment** is symptomatic

DISEASES CARRIED BY BLOOD SUCKING INSECTS

In the previous section were described diseases in which certain insects transmitted the virus from lower animals to man, or from man to man, without, however, necessarily directly inoculating the new host Blood sucking insects, on the other hand, introduce the virus into the human blood stream through their capacity of penetrating the skin and injecting the virus Diseases so inoculated do not necessarily pass through an intermediate host except the insect There is also another important difference, whereas the biting insects are usually associated with filth and body uncleanliness, the blood sucking insects are dependent more upon a neglect of community rather than personal hygiene

Malarial Fevers

Synonyms—Malaria ague, chills and fever

Definition—Malaria is a specific infectious disease having an acute onset with chills and pyrexia which recur at regular intervals, or the pyrexia is continuous with marked remissions It may assume a rapidly fatal or pernicious form

Incidence—Malaria was common seventy five to one hundred years ago in European countries such as Italy France Germany, and England and throughout the northern United States It is now chiefly confined to tropical and subtropical countries being prevalent in India Burma Africa China Russia tropical Australia and the Indies the southern portions of the United States and Central and South America In those areas where there is a heavy rainfall it is particularly common and from time to time the mortality and morbidity are extremely high

Etiology—Although there are five or six clinical varieties of this infection, with considerable overlapping and divergence of signs and symptoms, there are really only three varieties of this parasite each one of which is usually accompanied by a rather clear cut clinical picture but their combination may lead to confusion in the correlation of the clinical pattern and the etiological agent

(a) *Tertian* malaria due to *Plasmodium vivax* and *Plasmodium ovale*
(b) *Quartan* malaria due to the *Plasmodium malariae*
(c) *Aestivo-autumnal* malaria due to the *Plasmodium falciparum*

It is usual to refer to these several plasmodia as the tertian, quartan, or aestivo autumnal parasites. They belong to the division Protozoa, class Sporozoa, order Haemosporidia, and genus Plasmodium. They are all closely related but have certain distinguishing morphological characteristics which can usually be recognized by those who have expert knowledge.

The parasite is inoculated through the skin by the female mosquito of the genus Anopheles. Man acts as the intermediary host while the mosquito is



Fig 491 —*Plasmodium vivax* (Tertian plasmodium) 1 Young forms or the so called ring forms ×1500 2 Quarter grown parasite ×1500 3 Half grown parasite ×1500 4 Three quarters grown parasite ×1500 (Photomicrographs made at the U S Army Medical Museum)

the definite host All of these parasites go through a similar cycle in man where they reach maturity and reproduce After inoculation they appear first attached to the erythrocyte as a small yellowish protoplasmic mass with a nucleus rich in chromatin These are called the merozoites They are about $\frac{1}{5}$ to $\frac{1}{10}$ the size of an erythrocyte and soon penetrate it The tertian is

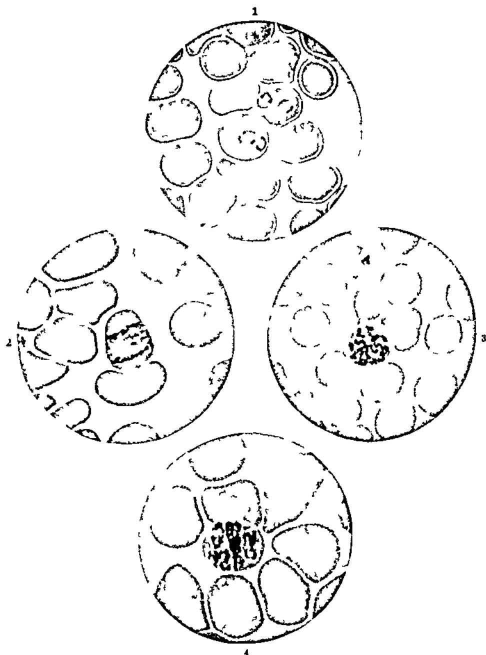


Fig 492—*Plasmodium malariae* (Quartan plasmodium) 1 Young parasites the so called ring forms ×1800 2 Half grown parasite the so called band forms ×1800 3 Three quarters grown parasite ×1800 4 Large band form ×1800 (Photomicrographs made at the U S Army Medical Museum)

irregular and may be ameboid When stained within the cell they have a general appearance of a signet ring They gradually enlarge and brownish pigment appears within them in about 12 to 15 hours This can be recognized

in fresh specimens and appears motile It is apparently obtained from the hemoglobin This pigment increases in amount with the parasitic growth, and the nucleus at the same time becomes polymorphous and begins to show segmentation The tertian parasite grows more quickly than the quartan and at the end of 30 to 70 hours, depending upon the variety, it occupies the area of the whole erythrocyte which now may appear as a thin envelope The divisions of the parasite become complete, each containing a small nucleus

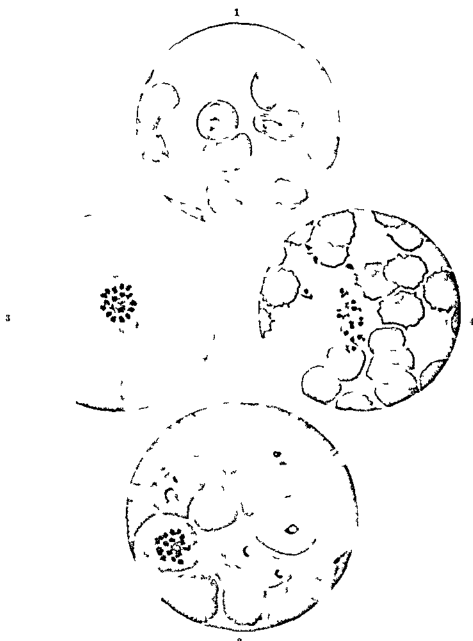


Fig 493 —*Plasmodium falciparum* (Aestivo autumnal plasmodium) 1 Young parasite The so called ring form ×1800 2 Sporulating parasite and several young ring forms ×1800 3 Sporulating parasite ×1800 4 Free spores or merozoites ×1500 (Photomicrographs made at the U S Army Medical Museum)

These are called rosettes and number 8 to 32 merozoites The envelope ruptures and these are set free in the blood stream, each in time attaches itself to another erythrocyte, and so the reproduction continues If it were not for the phagocytic power of the leucocytes and the cells of the reticulo endothelial



Fig 494.—*Plasmodium falciparum* 1 Phagocyte 2 The female crescent or gamete (macrogametocyte) ×1500 (macrogametocyte) ×1500 3 The female crescent or gamete (macrogametocyte) ×1500 4 The male gamete or crescent (microgametocyte) ×1500 (Photomicrograph made at the U S Army Medical Museum)

system, they would soon multiply to enormous numbers The only ones that escape destruction are those that become attached to and invade an erythrocyte The malarial parasite does not choose to remain in the circulating blood if avoidable, but would rather rest in the spleen bone marrow or liver, on

account of the slow circulation and fortunately this is where the reticulo endothelial system is most abundant This asexual cycle usually occupies a consistent time period for the various parasites the tertian, 48 hours the quartan 72 hours and the aestivo autumnal, 24 to 48 hours After a few days sexual forms make their appearance, and the male and female can be dif ferentiated by those with experience The sexual forms are called gametocytes or gametes In the tertian and quartan malarias these are rounded or oval

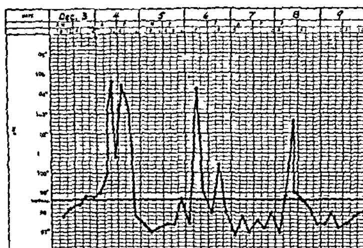


Chart XXXVII — Temperature chart of simple tertian malaria

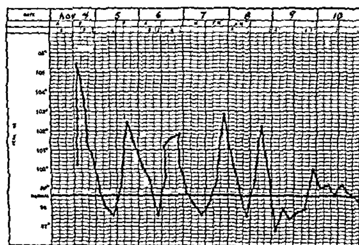


Chart XXXVIII — Temperature chart of a double tertian infection, showing quotidian type of temperature

ameboid and irregular while in the aestivo autumnal the ameboid movement and therefore the irregularity is very slight and they are usually oval or crescentric They live for two to three weeks but are constantly being replaced

When the *Anopheles* sucks blood containing gametes into its stomach the male (microgametocyte) produces long flagellae which break off and invade the female (macrogametocyte) which is then fertilized and the cycle of reproduction is started The fertilized zygote now progresses by ameboid move

ment through the stomach wall to its outer surface in the abdominal cavity It rapidly grows in size and at the end of 15 to 25 days is a large oocyst containing numerous spindle shaped bodies which are a small protoplasmic

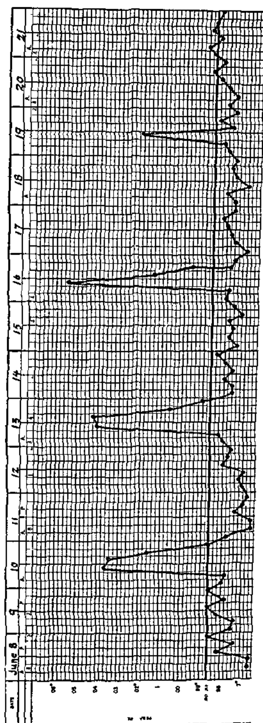


Chart XXXIX.—Temperature chart of quartan malaria

mass and a nucleus The oocyst ruptures and the young parasites (sporozoites) are set free Some of these reach the salivary glands and are inoculated into the next victim bitten by the mosquito and so the cycle continues from man to mosquito, and from mosquito to man

Symptoms and Signs—Malarial fevers may be generally classed in two groups (a) those which have regular remittent bouts of pyrexia and (b) those where the pyrexia is continuous over irregular periods of time

The first group has given to these fevers a number of synonyms such as ague chills and fever, quotidian tertian, and quartan malaria The quotidian type is that in which chills occur every day and is caused by a double infection of the tertian parasite In tertian malaria the chill occurs every other day and in the quartan variety two days elapse between the chills A double quartan infection could produce a chill for two days in succession and then there would be a free day, while if there is a triple infection chills will occur daily as in the quotidian or double tertian type

The character of the chills is the same in all varieties of this infection There are certain prodromata such as headache, lassitude, yawning and sometimes nausea and vomiting Shortly after these symptoms have appeared the body temperature begins to rise The patient may be quite unconscious of this but soon he begins to shiver and before long a violent rigor ensues He feels intensely cold the skin and mucous membrane are pale and bluish, and the surface temperature is lowered Inspection of the capillaries of the nail bed under the microscope at this time shows these to be contracted and the blood flow extremely sluggish The body temperature by rectum is greatly elevated, at times to 106° F There may be delirium and in children convulsions This stage may last from a few minutes to an hour or more to be followed by a sense of intense heat the body surface is then erythematous and dry Whereas the pulse in the initial stage was small, it is now full and bounding There is great thirst, headache and active delirium The capillaries in the nail bed are dilated and *the blood flow is extremely rapid In from thirty* minutes to several hours perspiration begins which soon progresses to a drenching sweat The patient is now much relieved although exhausted, and as a rule passes into a deep sleep This is the description of a moderately severe paroxysm All cases do not necessarily conform to this general description as there are variations in degree rather than in sequence The whole paroxysm usually occupies from 8 to 12 hours and recurs with remarkable regularity at the same hour of the day during the height of the disease but as the infection is being overcome the intervals may become longer

Herpes labiales is common The liver may be enlarged and the spleen is palpable but during the intervals it may not be felt

In the second form there is a more continuous remittent fever and chills do not occur with any regularity although they may be present at the onset This type may be caused either by the tertian or the quartan parasite but it is most common when the infection is due to the *Plasmodium falciparum* or aestivo autumnal parasite which means summer' and autumn" when the disease is most common When due to the last parasite the onset of the pyrexia is as a rule gradual somewhat like typhoid fever, and chills are uncommon *It is in this type that the so called* pernicious' malaria occurs the name being applied to very severe forms which are probably due either

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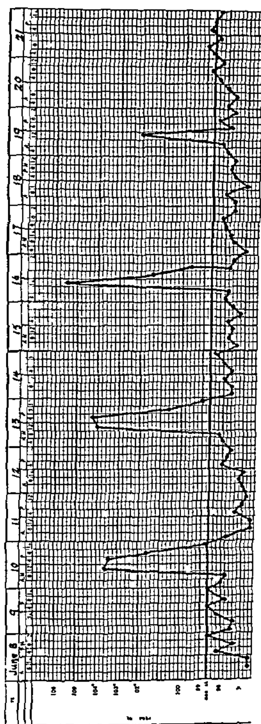


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to a lack of resistance of the host or to the concentration of the parasites in vital areas It is customary to recognize three forms

(a) **Comatose Type**—This is distinguished by severe symptoms in the central nervous system, especially violent delirium and coma It is supposed to be due to the cerebral capillaries being blocked by vast numbers of the parasites, in other words, they produce capillary thrombi in the cerebrum

(b) **Algid Type**—Here gastrointestinal symptoms dominate the clinical picture There is great prostration and asthenia, vomiting and diarrhea with melena being the chief features These symptoms are supposed to be due to the capillaries of the gastrointestinal tract being affected by the parasite in the same manner as the cerebral vessels are affected in the comatose variety

(c) **Hemorrhagic Type**—In malaria, hemoglobinuria is not an unusual event due to the destruction of enormous numbers of erythrocytes, but in this type there is gross interference with renal function The urine becomes darker and darker, although it may return to a normal color for a few days, but the abnormal appearance comes back with each succeeding bout of pyrexia There may also be suppression of urine Chills occur and are extremely violent although the temperature may not be high Anemia soon is conspicuous and there is a rapid loss of weight

In all severe malarial infections but particularly in the aestivo autumnal type, what is known as "malarial cachexia" may occur There are slight fever, anemia dyspnea particularly on exertion, edema, and hemorrhages into the skin and retina and the spleen is conspicuously enlarged With recurring attacks this condition is not unusual The anemia may be below 2,000,000 erythrocytes and normoblasts and spindle cells are frequently found A leucocytosis, although not usual, may occur during very severe paroxysms and may be as high as 20 000 due to an increase of the granulocytes and the large mononuclear cells

Pathological Anatomy—The most conspicuous anatomical change in malaria is found in the spleen which in fatal cases is enormously enlarged It is smooth and the capsule is thin In color it may be greyish to an absolute black The pulp is soft and the malpighian bodies are easily seen On microscopical examination the principal characteristic is the thickening and the swelling of the blood vessels which are often obstructed by massive collections of the parasites which are not only free in the lumen of the vessels but also are found in large numbers in the endothelial cells of the blood vessels and those of the reticulo endothelial system The liver is also enlarged and similar blockage of the small vessels and the endothelial and reticulo endothelial cells are gorged with parasites There is great congestion of the organ and deposits of pigment may be readily seen The kidneys brain and bone marrow are similarly affected, in fact the common anatomical change in all malarial lesions is the obstruction of the capillaries by the malarial parasites and their presence within the cells of the reticulo endothelial system and the endothelial cells of the blood vessels even in areas where the reticulo endothelial system is not supposed to be abundant The larger vessels may be affected in this manner as well as the smaller ones

Course—All patients who have had malaria are subject to relapses It is difficult, when they are living in a malarial district, to be certain whether these relapses are not reinfections, but in patients who have removed to an environment where malaria as a local disease is uncommon, relapses may occur after several years Without treatment the tertian and quartan types frequently recover spontaneously and practically always do if sufficiently treated but if the therapy is not continued to a conclusion, relapses are common when it is stopped Aestivo autumnal malaria is more persistent than the other two and does not recover spontaneously as frequently, but with treatment relapses are not so common The clinical features of a relapse are the same as in the original infection The secondary lesions or complications of malaria are attributable to the changes in the vascular system, and may be extremely numerous if all those reported are taken into consideration They are found particularly in the central nervous and hemopoietic systems and are represented by paraplegia, hemiplegias neuritis ataxia, disseminated sclerosis and anemia

Diagnosis—There is usually but little difficulty in the diagnosis of an acute case of malaria It is particularly to be differentiated from other tropical infectious diseases such as yellow fever relapsing fever and dengue, but in addition it may be confused with bacillary dysentery, septicemias of various types, typhoid fever and acute bacterial endocarditis The identification of the parasite in the circulating blood or by splenic puncture makes the diagnosis absolute If this confirmation cannot be obtained, it is often necessary to have recourse to the therapeutic test with quinine It is of more negative than positive value in that if the pyrexia does not disappear when the patient is taking quinine it is of more significance than if it does, which would not necessarily eliminate malaria Every effort should be made to detect the parasites before quinine is given because once this therapy has been started it is difficult to be certain whether the continued absence of the parasite is due to the quinine or whether some other febrile disease is present It must be appreciated that all cases of malaria do not necessarily follow the classical clinical description This is particularly so when due to the *P falciparum* when a great variety of clinical patterns may be encountered which may simulate practically any febrile illness It may be confused with subactive bacterial endocarditis miliary tuberculosis amebic abscess of the liver, typhoid fever etc

Prognosis—If treatment is started early and continued thoroughly in a mild or moderate case of malaria recovery occurs in approximately 100 per cent of the cases In tertian and quartan malaria the mortality is low even in untreated cases but in the aestivo autumnal variety if the treatment is insufficient or is long delayed the mortality rises rapidly in direct ratio to these two factors About 50 per cent of the deaths occur in the comatose type of pernicious malaria and the rest are accounted for by the algid and hemorrhagic types and malarial cachexia due to all types

Treatment—*Prophylaxis*—As malaria is spread by the Anopheles mosquito the principal method of prophylaxis is the extermination of this insect by drainage of all stagnant waters or if this is impracticable by covering them with oil so as to prevent the maturation of the larvae When extensive

operations of this manner are indicated, it may be impracticable therefore means to kill the larvae are used For this purpose an oily substance called "Malariol," which is effective in a high dilution when sprayed on the water, or Paris green may be used This is a public health problem in which, however, the physician should take an active part in education and propaganda In addition all houses should be screened, and if necessary bed nets should be used In latent cases treatment should be continued as these although not suffering clinically themselves are a source of reinfecting the mosquito which can then transmit the disease to a susceptible individual This is particularly important in the itinerant population, as a vagabond with latent malaria may reinfect districts in which this disease has been exterminated

The principal drugs used in the treatment of malaria are quinine and some of its alkaloids and several synthetic antimalarial agents The latter are atabrin hydrochloride (mepacrine hydrochloride) and atabrin musonate (mepacrine methane sulphonate) The latter is for parenteral use

There is not known at present any drug which can affect the sporozoite and therefore be a true causal prophylactic in therapeutic doses In the schizont stage both the drugs mentioned above are effective and therefore can be used to control the acute malarial attack Quinine is probably the most effective In the gametocyte stage quinine is the more effective particularly for *P vivax* and *P malariae* which produce benign tertian and quartan malaria but has little if any action on the crescents of *P falciparum* Therefore being a poor gametocide it has little value as a sterilizing agent in the carrier state The same may be said of atabrin however it has certain advantages as follows 1 It can be taken easily and without discomfort by mouth 2 There are few side effects 3 Black water fever is not a contraindication 4 It is secreted more slowly than quinine On the other hand it is in some ways inferior to quinine 1 Its initial action is slower 2 It may produce a yellow discoloration (not jaundice) of the skin 3 Rarely may produce a transient confusional psychosis

Suppressive Methods—During war when troops *en masse* are exposed to and contract malaria it has become customary to suppress the active symptoms by the use of quinine or atabrin (mepacrine) This therapy should be started before entering the malarial region and continued Atabrin has been chiefly employed There is some difference of opinion as to the dosage of atabrin for this purpose Some advise 0 1 gm on four days a week some 0 2 gm twice a week others 0 06 gm six days a week and still others 0 05 gm every day It would appear that these differences of opinion are immaterial and that the principal point to be borne in mind is a constant level in the blood therefore frequent use of small amounts is better than larger amounts at intervals It will be noted that these methods are not strictly prophylactic but suppressive, in other words they inhibit the symptoms of malaria becoming incapacitating and do not necessarily eradicate the plasmodia

Active Methods—The active treatment of malaria in the individual rests upon the continuous use of quinine in proper quantities until the disease is cured In the acute stages 30 grains (3 doses of 10 grains each) of quinine sulfate should be taken daily for at least four days This amount as a rule is sufficient to prevent paroxysms but not to effect a complete cure For the next three months 10 grains a day should be taken without intermission In

persons who have not had acute paroxysms but who are infected, only this portion of the treatment is necessary. The dosage for children is proportionate and is roughly as follows: under the first year, ½ grain; first year, 1 grain; second year, 2 grains; third and fourth years, 3 grains; fifth, sixth and seventh years, 4 grains; eighth, ninth and tenth years, 6 grains; eleventh, twelfth,

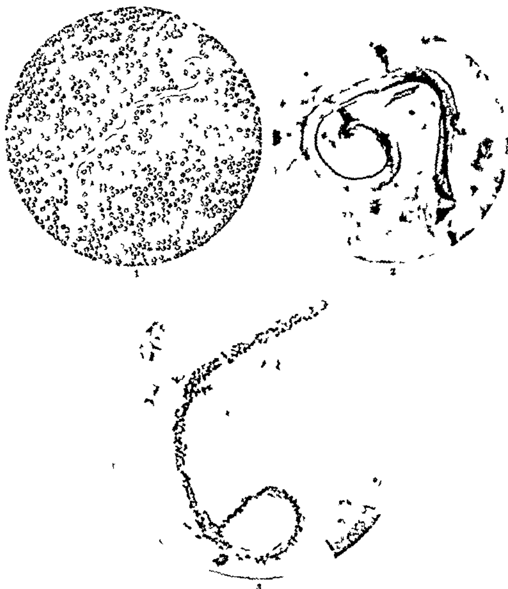


Fig. 495.—*Filaria bancrofti.* 1, *Microfilaria bancrofti.* Living specimen. 2, *Microfilaria bancrofti* contained within its sheath. 3, *Microfilaria bancrofti* after emerging from the sheath. (Photomicrographs made at the U. S. Army Medical Museum.)

thirteenth and fourteenth years, 8 grains; fifteenth year and over, 10 grains; all three times a day. Although it is quite clear that all patients do not require the same amount of quinine over the same period of time to effect a cure, it is impossible to forecast this in any individual case. Therefore it is best to be on the side of safety.

Other salts of quinine have been used but have no advantage over the sulfate which is undoubtedly the most effective In emergencies quinine may be given intravenously, but this method is not as efficacious in the long run as when taken orally A synthetic quinoline called "Plasmochin" has been used There is no doubt that it can cure malaria, but it is more common to use it in a combined tablet containing 1/6 grain plasmochin and 2 grains quinine Two such tablets are taken three times daily for a week with an interval of four to five days when the course is repeated, and so is carried on for five or six times That it has any particular advantage over quinine in the majority of cases is not proved It is a boon to those who have an idiosyncrasy for the latter Atabrin kills the tertian and quartan plasmodia but not the gametocytes of the aestivo autumnal plasmodia There fore to destroy these it must be combined with or followed by plasmochin

During World War II extensive and intensive work was done on newer chemotherapeutic antimalarial drugs This was of particular importance on account of the scarcity of quinine It also stimulated a more thorough in vestigation of atabrine both as a suppressive and as an agent in the treatment of the acute attacks and relapses Out of the former work *chloroquine* 7 chlo ro 4(4 diethylamino 1 methylbutylamino) quinoline was found in experimental animals to be much more effective than either quinine or atabrine Although it will not prevent an infection, it will terminate an acute attack and is a good suppressive As a cure the combination of a plasmochin like substance (6 methoxy 8 15 iso propylamino amylamino quinoline) combined with quinine has given great promise These compounds are not now readily available, so time will prove their worth

The general treatment of malaria is the same as in any other acute in fectious disease The complications usually recover spontaneously or if not nothing can be done for them but what would be indicated in a symptomatic form Hemoglobinuria is still the subject of debate as to its proper treatment It is claimed by some that quinine aggravates this condition, while there are others who are strong advocates for its use It is true that quinine may pro duce hemolysis if taken in sufficiently large quantities or in those who are peculiarly susceptible Therefore quinine should be given in smaller amounts than outlined above until the hemoglobinuria has disappeared

Filariasis

Definition—Filariasis is a specific disease caused by the invasion of nematode worms called filariae These worms enter the blood stream as embryonic forms called microfilariae transmitted by the mosquito Of the four species found in man there is only one, namely *Filaria (Wuchereria) bancrofti* which causes important pathological lesions The others *Filaria loa*, *Filaria ozzardi*, and *Ancanthocheilonema perstans* are of little importance as only one of them the *Filaria loa* sometimes may produce disabling conditions It is called the "eye worm" of West Africa and causes "calabar swellings" The principal lesion produced by the *Filaria bancrofti* is a blockage of the lymphatic channels leading to a lymphatic edema *(elephantiasis)* or chylous transudate

Distribution—This infection has a wide geographical distribution It is still found in the southern states of the United States, but is much more prevalent in certain parts of the West Indies, Africa, the East Indies and the Pacific Islands It is also found in northern Australia and has a wide distribution in northern South America

Etiology—The disease is caused by the *Filaria bancrofti* which is a nematode worm In its adult form the female measures 50 to 100 mm in length, and 0 2 to 0 3 mm in width It has a simple head with two rows of small papillae It looks like a thin piece of wet catgut The uterus which consists of two tubes occupies the greater part of the body the eggs being formed in the posterior portion As they proceed forward to the vagina they grow rapidly and are discharged as microfilariae the chorionic membrane forming an enveloping sheath The microfilariae measure about 0 1 0 3 mm The infection is transmitted from man to man by means of the mosquito two varieties being chiefly accountable namely the *Aedes variegatus* in Polynesia, and the *Culex fatigans* in other countries The microfilariae are found free in the circulating blood and when the mosquito sucks blood from an infected person the microfilariae reach the mosquito s stomach where they shed their sheath and find their way into the thorax, becoming imbedded in the muscle fibers where they undergo considerable development, and after about twenty one days they migrate to the head and lodge in the proboscis When a mosquito attacks man, the parasites are lodged under the skin, or may even penetrate into the blood and lymphatic channels Many of these parasites may remain about the portal of entry They are carried by the lymphatic and blood streams to far distant parts of the host and have a particular predilection for lymphatic channels and lymphatic glands They also have a tendency to collect in groups in localized areas of tissues

Except in Polynesia the *Filaria bancrofti* shows a definite periodicity The reason the Polynesian strain does not do this is unknown Although occasionally a microfilaria may be found in the blood stream during the day it is after 6 00 P M that they begin to increase in numbers and between 10 00 P M and 2 00 A M that they reach their maximum concentration and then gradually diminish in numbers again It has been suggested by Lane that this is due to a cyclical birth of microfilariae from the parent female

Symptoms—All patients infected with filariae do not necessarily suffer any inconvenience The association of these parasites with the lymphatic tissue however may produce a variety of conditions in different individuals There may be lymphangitis adenitis lymphedema or elephantiasis lymphatic varicosities, enlargement of the spermatic cord and epididymis chyluria and chylous exudate into the pleura peritoneum and pericardium or cysts may be formed in the skin glands and the breasts or other tissues The most characteristic features apart from the chyloform serous transudates are filarial lymphangitis and elephantiasis

Filarial Lymphangitis

This condition is ushered in by an acute pain in the limb or in superficial glands The pain is widely distributed and indefinite in localization but may

be more severe in one place than in another In twenty four to forty eight hours there is a chill with pyrexia, the latter continuing for about three days There are the usual signs of infection accompanying it, such as headache, malaise, nausea, and vomiting Shortly following the chill, streaks or patches of erythema may appear on the skin outlining the superficial lymphatics, or a confluent area of lymphatic inflammation which may cover quite a large area It is exquisitely tender and painful The erythema shades off into the surrounding skin and has not a clear cut margin as in erysipelas These attacks vary greatly in intensity, some are mild and fleeting, while others are most intense In the latter there is sweating, great prostration, malaise and anorexia In a few days the whole inflammatory action seems to subside Recrudescences occur about every three weeks in most cases, but in some there may be an interval of many months Although the reaction usually recurs in the same place in each individual, this is not necessarily so Secondary bacterial infections are not uncommon and in such the general systemic reaction is relatively severe compared to the local lymphangitis

Elephantiasis

Elephantiasis is a condition of lymphedema It may occur following filarial lymphangitis or independent thereof (see above) At first there is an edema which pits on pressure but as time passes the swelling becomes more and more brawny and indurated This is not due to the lymphatic stasis, but results from fibrosis secondary to bacterial infection Elephantiasis usually occurs in the legs, scrotum penis, and vulva and may also be found in other parts of the body When there is elephantiasis with recurring attacks of lymphangitis it is commonly called "elephantoid fever" In such cases the part continues to enlarge, while in ordinary filarial lymphangitis the edematous area returns to its normal size

Abscesses in the skin or elephantoid tissue are quite common and are caused by pyogenic infection particularly the streptococcus and staphylococcus When these abscesses are opened, these organisms can be recovered in smears and culture There is however, another type which appears like a cold abscess, and when incised an odorless sterile pus is obtained In both types fragments of adult worms or microfilariae may be found

In association with involvement of the spermatic cord or epididymis with or without signs of acute inflammation a hydrocele may occur This is due to a filarial lymphangitis in these parts

Chylous exudate into the pleura pericardium or peritoneum results from a blockage of the lymphatic duct pleural or pericardial or mesenteric lymphatics, which leads to a lymphedema of the serous membranes Blockage of the renal or vesicle lymphatics produces chyluria and if hemorrhage also occurs it is called ' hematochyluria '

The microfilariae are frequently found free in the blood stream or in any of the areas of lymphangitis adenitis or lymphoid tissue During the acute

attacks there is a leucocytosis which may be as high as 40,000 per cu mm, and is chiefly composed of polymorphonuclear cells. After the exacerbation these decrease and an eosinophilia follows which may amount to from 20 to 30 per cent of the leucocytes.

Pathological Anatomy.—The anatomical changes in filarial infection are due to the obstruction of the lymphatics by the adult worms. They may also obstruct the blood vessels and may invade the sinuses of the lym-



Fig 496.—Elephantiasis of the scrotum. The patient was a cannibal chieftain. (Courtesy of Dr A M Fauntleroy, U S Navy. From Sutton and Sutton, Diseases of the Skin.)



Fig 497.—Elephantiasis of the leg of a forty year old Negro. (Courtesy of Dr W H Strother. From Sutton and Sutton, Diseases of the Skin.)

phatic glands. When they die in these situations they usually lead to a permanent obstruction, although many of them are dissolved and are finally absorbed. Others however are surrounded by a capsule of fibrous tissue which may in time calcify and then can be recognized by the x ray.

Diagnosis.—The recognition of this condition in endemic areas is not at all difficult and has only to be differentiated from acute septic lymphangitis or edema due to some local or general cause apart from filariasis.

Prognosis.—The prognosis of filariasis as to life is good, provided the filaria have not invaded some vital tissue. The principal danger arises from secondary infections.

Treatment.—*Prophylaxis*.—The prevention of this infection is the same as that described in other diseases such as malaria transmitted by blood sucking insects. The *active* treatment of this disease has not been satisfactory although many drugs have been employed. In Puerto Rico they have advocated the use of antistreptococcus and antiplague serum, and antityphoid vaccine. These have seemed to prolong the interval between the attacks. If the position of the worms can be recognized by x-ray much can be done through excision, but this is only effective when they are accessible. Amputation of elephantoid tissue of the scrotum has greatly relieved the local mechanical disability. Removal of lymphatic glands is not to be advised as traumatic elephantiasis may be added to the already existing condition.

Dengue

Synonyms.—Break bone fever, dandy fever.

Definition.—Dengue is an acute specific infectious disease caused by an unknown filterable virus which is conveyed from man to man by the *Aedes aegypti* mosquito. It is characterized by exquisite pain in the limbs, a biphasic pyrexia and a rash toward the end of the febrile period.

Etiology.—The filterable virus has not been discovered but it is apparently ultramicroscopic. The disease closely paralleled outbreaks of yellow fever (page 736) and the two diseases were often confused. They are both transmitted by the Aedes mosquitoes but by different varieties. In both there must be an interval of eight to twelve days between the infection of the vector and its capacity to transmit the disease to man.

Symptoms and Signs.—The incubation period is from three to fourteen days and the portal of entry is the skin via the mosquito bite. There is a sudden onset with pyrexia and chilliness, sometimes a rigor, considerable malaise and intense pains in the muscles and bones. Headache and pain in the eyes are severe. There is diffuse flushing and injection of the skin, conjunctivae, mouth and pharynx. The pyrexia continues for a few days (two to four) when it returns to normal and all the symptoms rapidly improve. The pyrexia returns in several days and the symptoms return with greater severity. During the first phase, the pulse is rapid while in the second it is relatively slow. There is an early leucopenia with a relative lymphocytosis. Immature granulocytes are present and the mature ones are much degenerated. The spleen is not enlarged. With the second bout of fever a rash appears. This may be scarlatiniform or morbilliform, or intermediate. It fades with the fall of fever and leaves a fine desquamation. The urine may contain a trace of albumin and a few casts but never approaches the abnormal findings of yellow fever. Jaundice does not occur.

Pathological Anatomy.—On account of the rarity of an opportunity for postmortem examination little is known of the anatomical changes produced by this infection. The few uncomplicated cases that have been examined

revealed general cloudy swelling of the viscera particularly of the liver which was also fatty and a few petechial hemorrhages chiefly in the gastrointestinal tract

Diagnosis—Dengue is to be differentiated from influenza rheumatic fever malaria and pappataci fever on account of the severe pains and the *leucopenia This seldom offers any difficulty* In the case of yellow fever the close similarity of many of the features which are common to both may and always have tended to confusion The cause the vector the onset the flushing and the pyrexia with the remission make them closely allied But the absence of jaundice hemorrhages and renal signs are against yellow fever while the pronounced leucopenia points to dengue

Course and Prognosis—Recovery usually has occurred by the eighth to tenth day but convalescence is tedious the pains often persisting for weeks and there may be considerable mental depression and insomnia The mortality is very low and occurs chiefly in the elderly or those suffering from chronic and debilitating illness

Treatment—*Prophylaxis* is the same as that employed in yellow fever or malaria The general treatment is symptomatic but morphia may be required to relieve the pains

Pappataci Fever

Synonyms—Phlebotomus fever sand fly fever

Definition—It is an acute specific infectious disease caused by a filterable virus transmitted by the sand fly *(Phlebotomus papatassii)* and characterized by pyrexia malaise and leucopenia

Etiology—The filterable virus is carried by the sand fly a minute hairy insect which can pass through an ordinary screen or net All sand flies are not vectors the particular one in this case being the *Phlebotomus papatassii* As Leishmaniasis is also transmitted by a variety of sand fly it is better that this name should not be used The female sucks blood and to transmit the disease she must bite a patient during the first two days of illness and six days thereafter she can infect others The bites often produce local irritation

Symptoms and Signs—The incubation is from four to ten days and the portal of entry is through the skin The onset is sudden with pyrexia and a *chill headache and pain behind the eyes in the back of the neck* and legs are prominent The face is flushed and the mucous membranes of the mouth and pharynx and conjunctivae are intensely injected There is a pronounced neutropenia There is no eruption The fever lasts usually about three days although sometimes longer and rapidly returns to normal The patient is usually much depressed during convalescence and there is a conspicuous bradycardia Recovery always occurs and there is a short period of immunity then reinfection may occur

Diagnosis—This disease may be confused with other febrile illnesses such as influenza malaria etc but the true cause in this instance is soon found It is more difficult to differentiate it from dengue in which there is also a leucopenia but the severity of pain and the eruption in the latter are distinctive

Treatment—*Prophylaxis*—Protection from sand fly bites is the only method of prevention, as sand flies are almost impossible of extinction Therefore fine netting (1 5 mm or less mesh) must be used in all ground floor windows and doors or as protection during sleep The usual applications to the exposed parts to keep insects away may be used

There is no specific treatment, which should therefore be symptomatic

LEISHMANIASIS

There are three diseases caused by different varieties of this protozoan parasite which belongs to the flagellata of the genus *Leishmania* They are all conveyed to man, although perhaps not exclusively, by different sand flies Two might be classified as local lesions, namely, oriental sore and espundia while the third kala azar, is a more systemic infection The three varieties of *Leishmania* closely resemble each other Each has two phases in its life history On culture media and in the vectors they are flagellated, have a fusi form shape and with Giemsa stain blue with a relatively large red nucleus In man they are aflagellate and are chiefly found within the endothelial and mononuclear cells where they multiply and eventually rupture the cell from which they escape to invade others When they are taken into the intestine of certain insects the flagellate forms again appear These multiply and eventually are infective to man

Oriental Sore

Synonyms—Cutaneous Leishmaniasis Aleppo sore frontier sore, tropical sore Aleppo boil Delhi boil

Distribution—Oriental sore is found in the islands of the Mediterranean, Asia Minor Northern Africa, Syria, the Arabian Peninsula, Mesopotamia Persia, India Turkistan and Nigeria

Etiology—This infection is caused by the *Leishmania tropica* It is trans mitted by the sand fly, *Phlebotomus papatassii*, which is likewise the vector for pappataci or sand fly fever It also occurs in dogs in endemic areas It is prevalent in the natives of these areas in both sexes and all ages

Symptoms—The incubation period is indefinite from a few days to months The onset is characterized by single or multiple papules which gradually enlarge and are covered by scales A serous exudate soon appears and the surface becomes moist and a small ulcer is produced This has a sharp margin and slowly extends The edges become raised and the surround ing tissue indurated Secondary ulcers may form either through multiple original infections, or by direct seeding The virus may also be trans mitted from man to man The primary nodule may disappear without ulcer ating, or the local lesion may acquire a verrucose lupoid or keloid character There are few if any general symptoms The duration of the primary lesion varies greatly The ulcers may remain as granulating areas for periods of months or even more than a year and healing leaves a deeply pigmented re tracted scar Secondary infections modify the course considerably in that

they may make a local lesion much more severe and destructive, or give rise to symptoms of a generalized infection

Diagnosis—*The diagnosis is made by examining the discharge of the ulcerated area, or better that obtained by puncture of the surrounding induration The parasites will be found in endothelial and large mononuclear cells and will readily stain by Giemsa* They may also be grown on N N N and other culture media at 22° C The former consists of agar 14 grams salt 6 grams distilled water 900 c c and ⅓ as much defibrinated blood as agar is added at 52° C and allowed to cool

Prognosis—The prognosis from the local lesion is good as it is never fatal Death occurs only from severe secondary pyogenic infections



Fig 498—Photograph of a case of cutaneous Leishmaniasis—oriental sore (Courtesy of Dr J L Todd)

Treatment—*Prophylaxis* is accomplished by avoidance of being bitten by *the sand fly but this is almost impossible among the natives* When the primary sore occurs it should be treated as any ordinary infected area The disease is *promptly cured by antimony which is given intravenously in a 2* per cent solution of sodium or potassium antimony tartrate or tartar emetic The first dose is usually 2 c c and it is increased by 1 c c every other day until 5 c c are being injected This is the maximum amount and should be continued until 4 grams of the drug have been administered Other forms of antimony such as Neostibosane and Ureastibamin (pentavalent compounds) have also been used with success (see page 1389) Other drugs have been advocated but it is best to use the specific antimony Local treatment by *x ray has been brilliantly successful*

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lar over days or even weeks When the disease is established the pyrexia assumes a double daily rise The other symptoms are rapid anemia, leucopenia thrombocytopenia diarrhea emaciation edema and great enlargement of the liver and spleen There is an increase of plasma globulins while a reduction in the plasma albumin fraction is on the contrary so great that the total plasma proteins are conspicuously reduced which accounts for the edema (see page

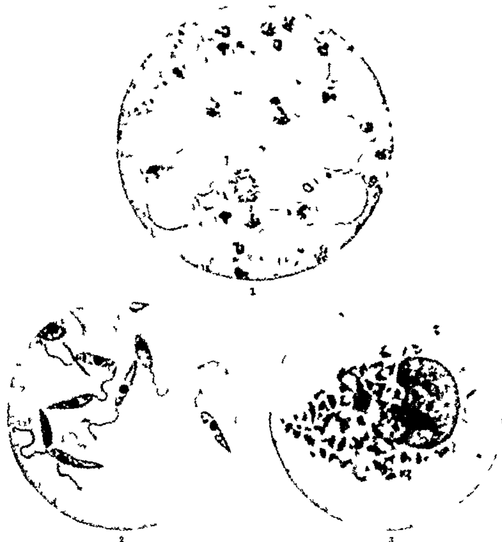


Fig 499—Leishmania donovani 1 In spleen smear from a case of kala azar ×1800 2 Flagellated form from a culture ×1800 3 L. tropica in a smear made from a tropical ulcer ×1800 (Photomicrograph made at the U S Army Medical Museum)

1256) The severity of the symptoms varies considerably from acute and fatal illness in a few weeks to a subacute and finally chronic type which may last for several years In children and infants the irregular pyrexia with progressive anemia lethargy emaciation purpura and splenomegaly are the principal features

In addition to the clinical picture outlined above many complications arise These are probably due to a hemorrhagic tendency and secondary infec

Espundia

Synonyms—Mucocutaneous Leishmaniasis, American Leishmaniasis, Brazilian Leishmaniasis, nasopharyngeal Leishmaniasis, uta, and forest yaws

Distribution—Espundia is found in the countries of Central and South America, as far north as Mexico, and as far south as the Argentine

Etiology—This disease is caused by the *Leishmania braziliensis* It is transmitted by the sand fly, *Phlebotomus lutzi* It is claimed by some authorities to be identical with *Leishmania tropica*

Symptoms—The incubation period is indefinite The inoculation usually occurs on an exposed portion of the body and appears as a primary papule which soon ulcerates It is indolent in healing, taking several months or years Toward the latter part of this period, or after it has healed a nodular thickening of the mucous membrane of the nose develops These nodules ulcerate and progressively invade the mucous membrane of the mouth, hard and soft palates, pharynx and larynx There may be deep necrosis and destruction of the nasal cartilages Untreated, the disease lasts for years and extensive destruction of tissue occurs in time

Diagnosis—The diagnosis is comparatively easy by demonstrating the Leishmania in smears of the exudate or tissue puncture

Prognosis—The prognosis for life is good as far as mortality from the immediate lesion is concerned, but secondary systemic infections leading to septicemia and pneumonia are the principal causes of death and before the specific treatment was discovered, the mortality from such secondary infections was very high

The *prophylaxis* and *treatment* are the same as for oriental sore

Kala Azar

Synonyms—Infantile splenomegaly, nonmalarial remittent fever, black fever visceral Leishmaniasis infantile splenic anemia

Distribution—This disease is endemic in the countries of the Mediterranean southern Russia India, Mesopotamia, China, Sumatra, and the head waters of the Blue Nile

Etiology—Kala azar is caused by the *Leishmania donovani* and in contra distinction to the two previous forms of Leishmaniasis the parasites are found in the circulating blood either free or in the leucocytes They are widely distributed in the endothelial cells of the internal organs particularly where the reticuloendothelial system is abundant—spleen, liver lymph glands, and bone marrow In man they appear as small, oval or round bodies 2 to 5 microns in diameter, which contain the minute rodlike body called the blepharoplast They are probably principally transmitted to man by the sand fly *Phlebotomus argentipes*, but experimentally it has been demonstrated that they can infect animals through ingestion of infected material and have been recovered from both the urine and the feces Dogs are naturally susceptible

Symptoms—The incubation period is indefinite and the onset is insidious with a progressive but irregular pyrexia This irregularity occurs not only during a single day but may assume a quotidian type or be altogether irregu

lar over days or even weeks. When the disease is established the pyrexia assumes a double daily rise. The other symptoms are rapid anemia, leucopenia, thrombocytopenia, diarrhea, emaciation, edema and great enlargement of the liver and spleen. There is an increase of plasma globulins while a reduction in the plasma albumin fraction is, on the contrary, so great that the total plasma proteins are conspicuously reduced, which accounts for the edema (see page

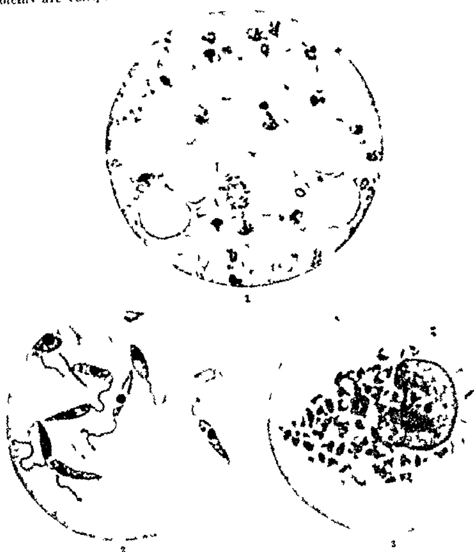


Fig. 499.—*Leishmania donovani.* 1, In smear of spleen from a case of kala-azar. ×1800. 2, Flagellated forms from a culture. ×1800. 3, *Leishmania tropica.* In a smear from a tropical ulcer. ×1800. (Photomicrographs made at U. S. Army Medical Museum.)

1256). The severity of the symptoms varies considerably from acute and fatal illness in a few weeks to a subacute and finally chronic type which may last for several years. In children and infants the irregular pyrexia with progressive anemia, lethargy, emaciation, purpura and splenomegaly are the principal features.

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is important, as a diffuse bronchitis leading to pneumonia sometimes complicates this treatment There may also be a papular eruption suggestive of the Brachmachari dermal Leishmaniasis mentioned above Kala azar does not respond to specific treatment as promptly as does espundia and oriental sore Several weeks usually elapse before the temperature returns to normal and more than one course may be required but the general condition of the patient rapidly improves In infants and children proportionate doses are employed ranging from 0 5 c c of a 2 per cent solution for infants (2 c c maximum dose) to 1 c c for a child of ten to twelve years (3 c c maximum dose) Ureastibamin and neostibosane (pentavalent antimony compounds) are more efficacious The usual dosage of the former is 0 1 to 0 2 gm intravenously every second third or four day until 1 to 4 gm in all are given Neostibosane may be given either intramuscularly or intravenously in dosage of 0 1 to 0 3 gm every other day or daily until 1 to 5 gm have been given The dosage and duration are varied according to the age and severity of the cases A vigilant follow up should be carried out with liver or spleen puncture if necessary to forestall recurrences and effect a cure

Trypanosomiasis

Trypanosomiasis may be of two clinical varieties They are caused by flagellate protozoa genera *Trypanosoma* and *Schizotrypanum* Two types of trypanosomes are found in Africa namely, *Trypanosoma gambiense* and *Trypanosoma rhodesiense* which are indistinguishable as are the clinical features except that the former tends to be more chronic than the latter They are both transmitted to man by Glossina (tsetse fly) chiefly the palpalis and morsitans There is also a South American variety which is due to the *Schizotrypanum cruzi* This is transmitted to man by a biting insect usually one of the *Triatoma* the commonest being the megista It is claimed by some to be inoculated from the crushed insect into scratches bite punctures or other abrasions while others claim it may be directly introduced into the blood stream at the time of the bite

African Sleeping Sickness

Synonyms —African trypanosomiasis

Distribution —The distribution of the infection due to the *Trypanosoma gambiense* is from Senegal to Angola on the west coast of Africa in the central portion contiguous to the lakes Victoria Albert and Banguelo the Belgian and Portuguese Congo French Equatorial Africa and in addition Western Mongolia and the islands of the Gulf of Guinea The *Trypanosoma rhodesiense* infests northeastern Rhodesia Nyasaland Portuguese East Africa and southern Kenya

Etiology —As these two trypanosomes are indistinguishable one description will serve for both They are found in the blood and the spinal fluid and stain readily with Giemsa They have a spindle shaped body mass the cytoplasm of which stains blue with a large oval red staining nucleus or trophonucleus This is situated at one end of the cell and also contains a red dot

tions Noma or cancrum oris (see Chapter II) is particularly common in children and is probably due to the pronounced neutropenia There may also be bleeding from the gums, purpura, cerebral hemorrhage, melena, and hematemesis while among the infections there may be bacillary or amebic *dysentery, septicemia bronchitis, pneumonia, otitis media mastoid disease,* etc A late complication or sequela is the development of cutaneous nodules in the skin which were first described by Brachmachari These are usually preceded by a leucoderma and follow the administration of antimony On biopsy, *Leishmania donovani* can be demonstrated and also grown from these tissues It has been suggested that this is a dermatological form, as the parasites cannot be demonstrated in the peripheral blood or in the spleen These cutaneous lesions often occur in groups

Diagnosis.—The direct diagnosis of kala azar depends upon the demonstration of the parasite either in the peripheral blood or in spleen, liver, or gland pulp obtained by puncture From such material they may also be grown on artificial media There are several tests which are an aid but are not absolutely diagnostic The first is the formal gel test advocated by Napier and Muir To 1 c c of the patient's serum a drop of 30 per cent formalin is added in two to three minutes the serum is completely jellied, and within twenty minutes is coagulated to a consistency of boiled egg white If the cases are under three months' duration there is first a cloudiness but the serum does not jell and in 24 hours is yellowish white The second test is the Brachmachari reaction which consists of adding one part of the patient's serum to 2 parts of distilled water a cloudiness and a precipitate appear The third test is the Chopra antimony reaction The patient s serum is diluted ten times with a saline solution and to this is added an equal part of 4 per cent antimony solution (ureastibamin preferred) A pronounced cloudiness appears

Kala azar is to be differentiated from malaria, tuberculosis, relapsing fever undulant fever and typhoid and paratyphoid fevers A careful analysis of the clinical picture and the employment of specific tests for these diseases seldom fail to indicate a proper conclusion

Prognosis.—The death rate from kala azar in untreated cases varies from 75 to 95 per cent Particularly is the mortality high in the acute variety or when cancrum oris secondary infections or hemorrhages develop Specific treatment has reduced the mortality to between 5 and 15 per cent but there are some cases which are resistant and these practically all die There is little doubt that mild cases recover although not recognized

Treatment.—The *prophylaxis* depends upon the segregation of the infected individual thereby preventing the vector (sand fly) from transmitting the disease, and finally the prevention or avoidance of being bitten by these insects as no means of exterminating them has as yet been discovered

The active treatment rests upon the use of the specific remedy, antimony either in the form of tartar emetic or preferably sodium or potassium antimony tartrate used in the same manner as that outlined for espundia In kala azar there is usually an exacerbation of the pyrexia after each treatment which may be accompanied by headache vomiting and cough The last symptom

looked for in the blood cerebrospinal fluid gland puncture juice and if not detected in smears animal inoculation should be carried out The disease in its early stages is to be differentiated from malaria typhoid fever and relapsing fevers

Prognosis —*If the infection is recognized in the early stages* and *proper* treatment is instituted the outlook is good If not even with treatment the eventual result is always in doubt and in untreated cases the mortality is practically 100 per cent

Treatment —The *active treatment* consists in the early use of arsenicals particularly atoxyl tryparsamide and Bayer 205 (germanin) Antimony preparations such as the trioxide tartar emetic or the double salt of antimony tartrate have also been employed In the more chronic stages tryparsamide is the drug of choice It should be given in 0 5 to 3 gram doses but never in amounts greater than 0 035 grams per kilo of body weight Four injections on alternate days are given and then a month s interval is allowed to elapse *before a second series is administered It may be necessary to continue up to* 15 or 20 courses Larger individual doses are apt to produce various toxic symptoms such as amblyopia optic atrophy jaundice etc such as have been noted in the treatment of syphilis by arsenic

Chagas Disease

Synonyms —Brazilian trypanosomiasis or schizotrypanosomiasis

Distribution —This infection is found in Peru, Brazil Panama and Venezuela

Etiology —It is due to the *schizotrypanosoma cruzi* This parasite is found in the circulating blood as a typical trypanosome but in the cells has a form resembling a *Leishmania It multiplies only in the cell and consequently* destroys it The trypanosomes free in the blood stream are about 30 microns in length and contain a large blepharoplast a nucleus and have an undulating membrane and a free flagellum In the cells however in the form of Leishmania they measure 2 to 5 microns and have only a nucleus and blepharoplast

Symptoms —There is an acute and a chronic form The former is most commonly found in children with pyrexia and after about 2 weeks there is a tissue pseudoedema caused by a deposit of mucoid material This does not pit on pressure but gives to the face and eyelids a swollen edematous appearance which closely resembles myxedema Of the viscera there is enlargement of the lymph glands liver spleen and thyroid and acute keratitis is quite characteristic The acute *stage lasts from 2 to 4 weeks and if untreated the* patient usually dies or lapses into the chronic state The latter is most common in adults The symptomatology depends upon localization of the trypanosomes and therefore myxedematous nervous cardiac thyroid suprarenal ovarian and *other* types have been described depending upon the principal situation of the organismal involvement

Pathological Anatomy —The anatomical changes result from the Leishmania destroying the invaded cells They are most frequently found in those tissues described above which have given names to different subvarieties but they may be also found in any tissue

or blepharoplast to which is attached a single flagellum which tapers out from an enveloping membrane but is free at the anterior extremity. They measure from 15 to 30 microns in length, and 1.5 to 2.5 microns in width. They increase through binary longitudinal division. In the fresh blood smears they are actively motile.

Symptoms.—The incubation period is from 10 to 14 days for the *Trypanosoma rhodesiense*, and that of the *Trypanosoma gambiense* 2 to 4 weeks. The onset is rather insidious with irregular pyrexia, lymphadenopathy, splenomegaly, asthenia and a fleeting erythematous rash. Localized or widespread edema soon appears. In the more chronic stages symptoms referable to the central nervous system are conspicuous. There is intense headache, mental lethargy, physical asthenia, and progressive somnolence. There may be retraction of the head, opisthotonos, local paralysis, convulsions, incontinence of urine and feces, coma, with succeeding death. In the advanced stages there is pronounced anemia. Iritis, cystitis and chorioretinitis are common in the chronic cases. The infection by the *Trypanosoma rhodesiense* is much more acute and severe than that of the *Trypanosoma gambiense*; it may last for several weeks. Occasionally mild cases are found.

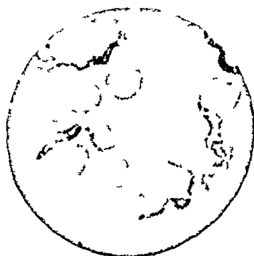


Fig. 500.—Trypanosomiasis. *Trypanosoma gambiense*. The sleeping sickness trypanosome. ×1400. (Photomicrograph made at the U. S. Army Medical Museum.)

Pathological Anatomy.—The principal anatomical changes are found in the lymph glands, which are enlarged, particularly the submaxillary, bronchial, mesenteric, inguinal and femoral. There is hyperplasia of the lymphoid tissue and trypanosomes may be found here as well as in the connective tissue of any organ, and particularly in the central nervous system, where the spinal fluid is found increased in amount, turbid from increased cells, the number of which give a rough index of the degree of cerebrospinal involvement. The fluid often contains trypanosomes. In protracted cases a chronic leptomeningitis occurs.

Diagnosis.—There are few diseases in which an early diagnosis is so important as in trypanosomiasis, as the eventual success of the treatment is greatly influenced thereby. In all suspected cases the parasite should be

be a comparatively rare disease, but this is quite wrong, for although it does not occur in epidemic proportions, it is endemic in many countries of which North America is not an exception, and unless prophylactic vaccination is maintained in a high percentage of the population epidemics are to be expected in the future

Etiology—Up to recent years the cause of smallpox was unknown, but now there is sufficient evidence to warrant the statement that it is due to a filterable virus This can be transmitted by the washings of the nose and nasopharynx the fluid of the vesicles and the dried exudate of the scabs, but so far it has not been transmitted by blood or serum Inclusion bodies in the cytoplasm of the epithelium of the skin were first described in 1892 by Guarnieri, and it is still debatable whether these represent the virus itself or the result of cellular reaction to the virus There are also found intranuclear bodies, and the exact role of these in the etiology is still in doubt

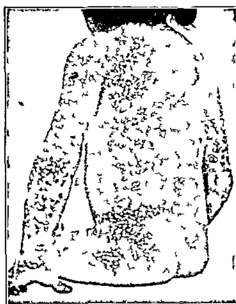


Fig 501 — Variola (Courtesy of Dr Jay F Schamberg From Sutton and Sutton Diseases of the Skin)

Symptoms—The incubation period is between ten and twelve days Although longer and shorter periods have been recorded it is doubtful whether these are accurate The onset is sudden with chills and severe pyrexia characteristic of many acute infections but in this disease are significant in their intensity There are exquisite headache severe pains in the extremities and in the lumbar region The last is more severe in smallpox than in any other infectious disease and is therefore considered to have some diagnostic significance The pyrexia soon mounts to 103 or 104° F and continues with little remission for two or three days During this time there may be scarlatiniform or morbilliform rashes which may be diffuse but more usually are confined to the area between the umbilicus and the midthighs Petechiae may also occur either in this area or elsewhere At the end of this period the temperature usually re

Diagnosis —This can be arrived at only by finding the parasite in the blood or the spinal fluid It is most frequently present in the former during the febrile attacks The diagnosis cannot be made with any accuracy on the clinical symptoms alone

Prognosis —The prognosis in well established cases is always grave in adults Children occasionally recover from the acute stage, but in chronic cases it is almost hopeless

Treatment —*Prophylaxis* —This is similar to all diseases transmitted by biting or blood sucking insects The isolation of the infected population is of greater importance if that be possible Unfortunately there is no specific treatment for this disease although the drugs outlined in the treatment of African sleeping sickness may be employed but the results have been most discouraging

INFECTIONS WITH AN UNCERTAIN PORTAL OF ENTRY

All infectious diseases so far described have had a fairly definite portal of entry, and in many of them the causative agent has been known or surmised There remains now to describe a number of infections the portal of entry of which would seem most probably to be through the nasal mucous membrane These are smallpox or variola varicella, or chickenpox herpes zoster, infectious mononucleosis epidemic pleurodynia swineherd's disease and leprosy It is interesting to note that among the Chinese a favorite site for the inoculation of the virus of smallpox or cowpox, to induce a protective immunity, is through the nasal mucous membrane In regard to leprosy there is little to indicate where the bacilli gain entrance but it has been suggested that the most likely portal is through the mucous membrane of the nose or nasopharynx

Smallpox

Synonym —Variola

Definition — Smallpox is an acute infectious disease caused by a specific filtrable virus It has an acute onset with headache pain in the back and soon develops a characteristic vesicular eruption

Epidemiology —Smallpox is one of the most infectious of diseases and is transmitted in the early stages by air borne droplets of nasal secretion, and in the later stages by the dried particles from the scabs of the eruption The virus can be transmitted directly from man to man or by household utensils or clothing, and epidemics have been recorded as beginning from bodies of smallpox victims recently buried and disinterred

Up to recent times periodic epidemics of this disease have occurred, sometimes covering large areas The virulence varied considerably not only in different epidemics but in different periods of an epidemic Before protective vaccination was more uniformly introduced the incidence was highest in children, as adults had practically all been exposed and had probably contracted a mild unrecognized infection or had obviously had the disease It was most disastrous in communities or races in which the disease had not been present for some decades or which had never been exposed It is supposed now to

hard but within a few days develop an umbilicated vesicle surrounded by a small red areola. These are multilocular as they do not collapse with a single needle prick. After another two or three days the vesicles become pustular, and the umbilication disappears. They gradually shrivel and about the twelfth day have dried up, producing scabs which soon desquamate. If the pustular eruption has been confluent, large areas of skin may be shed in one cast. The depth of the pustular ulceration is usually sufficient to leave definite pitting and scarring. This is aggravated by scratching which is difficult to prevent because of their intense itchiness.

The variable character of the eruption has given rise to a number of clinical forms of this disease. If it does not become purulent it is called "abortive," while if the eruption is scanty and leaves little or no pitting, it is called "varioloid." When there are hemorrhages into the skin and mucous membranes it is called "black" or "hemorrhagic" smallpox. The appearance of petechiae in the early stages indicates the probability of this type developing later, which is probably due to an intense toxemia affecting the permeability of the capillaries as in some forms of purpura, and in such hemorrhages from the mucous membranes of the mouth, stomach and bowel are not uncommon.



Fig. 94.—A single pustule which developed following vaccination. The patient, a man aged twenty-three, had never before been vaccinated. (Courtesy of Dr. E. L. Stewart. From Sutton and Sutton, Diseases of the Skin.)

With the pustular stage of the eruption the pyrexia returns and its severity is in proportion to the extent of the suppuration and continues until desiccation begins when it may fall either by lysis or crisis. This secondary fever is attributed in most part to the pyogenic infection of the skin. In direct proportion to the extent of the eruptive lesion there may be intense toxemia, delirium and edema of the skin, particularly of the face and eyelids. When the mucous membranes of the mouth, pharynx and larynx are involved there is considerable pain in these parts and a change in the voice may be noted. There is usually a general adenopathy, particularly in the cervical region, and the liver and spleen are palpable.

The urine is highly colored, reduced in amount as in all infections unless large amounts of fluids are taken. There is a leucocytosis which is in proportion to the pustular eruption and may rise to 30,000 or 40,000 per cu mm. It is principally due to an increase of the polymorphonuclear cells. In the severe toxic cases, particularly those with hemorrhage, a relative neutropenia may be found, probably due to a toxic effect upon the bone marrow. In all cases there is a thrombocytopenia, but this is only pronounced in the purpuric cases and may have some role in the causation of hemorrhages.

The visceral organs are seldom involved in smallpox. The renal changes, as already noted, are merely those of a general infection. Such secondary

turns to normal with a great improvement in the patient's general condition, and at the same time the *preliminary* eruption appears over the wrists, forehead and face. The *hands* and feet, particularly the palms and soles, seldom escape. This consists of reddish macules up to 3 mm *in diameter*



Fig 50 —Discrete smallpox in an unvaccinated female (Courtesy of Dr Samuel Sweitzer From Sutton and Sutton *Diseases of the Skin*)



Fig 503 —Variola of the confluent type (Courtesy of Dr Watson Campbell and Dr C S. Newman From Sutton and Sutton Diseases of the Skin)

which pale somewhat on pressure. The eruption soon becomes papular and rapidly spreads over the trunk and limbs and may appear on the mucous membrane of the mouth, nasopharynx, and nose. These papules are quite

hard but within a few days develop an umbilicated vesicle surrounded by a small red areola These are multilocular as they do not collapse with a single needle prick *After another two or three days the vesicles become pustular, and the umbilication disappears* They gradually shrivel and about the twelfth day have dried up producing scabs which soon desquamate If the pustular eruption has been confluent, large areas of skin may be shed in one cast The depth of the pustular ulceration is usually sufficient to leave definite pitting and scarring This is aggravated by scratching which is difficult to prevent because of their intense itchiness

The variable character of the eruption has given rise to a number of clinical forms of this disease If it does not become purulent, *it is called "abortive", while if the eruption is scanty and leaves little or no pitting it* is called "varioloid" When there are hemorrhages into the skin and mucous membranes it is called 'black' or hemorrhagic smallpox The appearance of petechiae in the early stages indicates the probability of this type developing later which is probably due to an intense toxemia affecting the permeability of the capillaries as in some forms of purpura and in such hemorrhages from the mucous membranes of the mouth stomach and bowel are not *uncommon*



Fig 504 — A single pustule which developed following vaccination The patient, a man aged twenty three had never before been vaccinated (Courtesy of Dr L. L. Stewart From Sutton and Sutton Diseases of the Skin)

With the pustular stage of the eruption the pyrexia returns and its severity is in proportion to the extent of the suppuration and continues until desiccation begins when it may fall either by lysis or crisis This secondary fever is attributed in most part to the pyogenic infection of the skin In direct proportion to the extent of the eruptive lesion there may be intense toxemia delirium and *edema of the skin particularly of the face and eyelids* When the mucous membranes of the mouth pharynx and larynx are involved there is considerable pain in these parts and a change in the voice may be noted There is usually a general adenopathy particularly in the cervical region and the liver and spleen are palpable

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The visceral organs are seldom involved in smallpox The *renal changes* as already noted are merely those of a general infection Such secondary

lesions as do occur can all be accounted for by a bacterial septicemia and include bronchitis, bronchopneumonia, arthritis, osteomyelitis, otitis media, keratitis, and furunculosis Quite separate from these secondary pyogenic infections are a group of lesions analogous to the involvement of the nervous system in other virus diseases, such as poliomyelitis herpes zoster, encephalitis, and include peripheral neuritis, myelitis, hemiplegia, and other focal cerebro spinal lesions

Smallpox is one of the few diseases which has been demonstrated to affect the fetus *in utero*

Pathological Anatomy—The principal tissues involved in smallpox apart from the skin are the blood vessels and the reticuloendothelial system In the skin there is a degeneration of the cells of the lower layers of the epidermis in which the inclusion bodies can be found, and in the exudate of the eruption the virus is contained in great concentration There is also conspicuous proliferation of the reticuloendothelial tissues, and it has been suggested that this has a relation to the hemorrhagic tendency Also the widespread involvement of the bone marrow is a prominent feature in this disease The liver and spleen are enlarged, particularly in children

Diagnosis—It is most important that a correct diagnosis of smallpox should be arrived at before the eruption has appeared During an epidemic this is comparatively easy It is in sporadic cases, however that there is great danger of their being the cause of a severe epidemic It must be differentiated from influenza, measles, dengue and epidemic meningococcal meningitis There may be considerable pharyngitis and with the preliminary rash may lead to confusion with scarlet fever or measles or with erythematous rashes which so frequently accompany a streptococcal sore throat The principal features in favor of smallpox are the fact that the patient has not been vaccinated the intensity of the onset, the constant occurrence of exquisite headache and pain in the back, but these symptoms are not particularly distinctive Therefore in isolated cases it is usual for the proper diagnosis to await the eruption At this stage the principal disease from which smallpox should be differentiated is chickenpox or varicella and particularly is this important in the mild cases of the former The onset of chickenpox is less explosive constitutional symptoms are mild the eruption appears on the first day and in distinction to smallpox it develops in successive crops Therefore macules papules vesicles and pustules may be present at the same time In smallpox the eruption follows a regular sequence and is practically the same in its entire distribution at the different stages In chickenpox the vesicles are unilocular and are not umbilicated The papules are soft as compared to the hard shotty primary eruption of smallpox Further the eruption in chickenpox lasts about three days If there is any doubt the patient should be rigidly isolated Other bullous eruptions that may be confused with smallpox are bullous syphilides impetigo contagiosum pemphigoid lesions and drug rashes

Prognosis—This depends to a great extent upon the character of the epidemic and whether or not the patient has been vaccinated, and how many

years previously In the unvaccinated the mortality has varied from 30 to 60 per cent, *while in the vaccinated, although they may contract the disease* it is usually of the abortive or varioloid form An early purpuric eruption is of serious significance as is also a confluent eruption which leads to extensive destruction of the skin surfaces and massive absorption of septic material *A scant or discreet eruption indicates a good result*

Treatment—*Prophylaxis*—The best prophylaxis is compulsory vaccination of children during their first year and this should be repeated every five to ten years The great danger of an epidemic arises from a mistaken diagnosis of a case in an unvaccinated community *Once the disease has been* recognized, the patient or patients should be strictly isolated and the health authorities in all contiguous communities should be notified The attendants upon these cases should also be isolated in the same building with the patients *and should not be allowed to intermingle at any time with the rest of the* population

Vaccination—From ancient times there are records of attempts to produce mild infections of smallpox through artificial inoculation under selected *conditions It has already been noted how the Chinese introduced infected* material into the nose In India the infective material was applied to the skin and the Persians ingested the crusts It was in eastern Europe (Turkey) that the infected material was first introduced into the skin by scarification *Although these methods were at times quite successful the risk was great* but perhaps not greater than the risk of ordinary contagion In the eighteenth century it became common knowledge among farmers that individuals who had contracted cowpox did not contract smallpox and this became a domestic manner in which smallpox could be prevented Jenner hearing of this undertook the inoculation of the cowpox infected material into humans and published his first results in 1798 There now seems little doubt that the virus *of cowpox and that of smallpox are identical* For many years the virus was transferred from man to man The first refinement was the collection of the vesicular fluid which was dried on small sharp instruments usually made of ivory which were called vaccine points With the discovery of the role of bacteria *in infection aseptic methods were introduced and now the* fluid for vaccination is prepared under the most rigid aseptic precautions from infected calves The virus for vaccination is also cultivated on the allantoic membrane of the chick *The favorite site for the inoculation is the upper and* outer aspect of the left arm but for cosmetic reasons this has been changed to the outer and upper aspect of the thigh in the female At the selected spot for vaccination the skin is sterilized and under aseptic conditions the superficial layers of the skin are scratched with a needle *It is inadvisable to produce* deep excoriations but just sufficient for serum to appear A drop of vaccine is placed on this area and allowed to dry Dressings or protective *shields are not advisable as they restrain the individual from* local cleanliness and are more likely to promote infection than to prevent it About the fourth day one or more small papules develop Vesicles appear on the next day and at this time there may be slight pyrexia and the spleen may be felt Surrounding the vesicle there is an erythema *and secondary vesicles may*

develop The pyrexia continues to increase for two to three days, and by the eighth day reaches its maximum, when there is also a local adenopathy The local area has now become quite swollen and edematous and it is best to keep the arm in a sling, and the patient confined to bed By the eleventh or twelfth day the local lesion begins to recede, and the reaction rapidly fades to a dry, brown crust which separates from the skin at the end of the third week, leaving a depressed scar In other words a mild infection has been produced Rarely a diffuse eruption occurs This description applies to the more violent of reactions, many of them are extremely mild without any systemic disturbance or excessive local reaction It is best to vaccinate all children within the first year, and to revaccinate them before the end of the tenth although in revaccinated individuals a reaction or "take" may not occur The milder the reaction the more rapidly does it develop and recede, indicative of an already existing partial immunity If no reaction occurs and the vaccination has been well done, it may be presumed that the patient is completely immune As the incubation period of smallpox is twelve to fourteen days, vaccination immediately after exposure is indicated

Vaccination has been criticized and the procedure attacked on account of the occasional sequelae Pyogenic infections may be severe and are of course due to faulty technic or lack of personal cleanliness Tetanus has also been reported and is due to the same causes Of a different order are the very occasional cases of encephalitis It usually appears on the tenth day after vaccination and would appear to be closely related to, if not identical with the encephalitic lesions associated with smallpox

The *active* treatment of smallpox is similar to that of any other acute infection The headache and pain in the back and limbs may be relieved by analgesics such as aspirin, phenacetine, and even morphine During the stage of eruption great care must be taken of the eyes, mouth throat and skin The former must be frequently irrigated with a mild antiseptic solution and oily sprays should be used in the nose and nasopharynx The care of the skin is more difficult Many measures have been advocated but most have been found to have little virtue The local irritations should be relieved by all means in our power but in confluent cases this is extremely difficult Scratching should be prevented by bandaging the hands Perhaps the most hopeful method of treatment is continuous warm saline baths but even here this can only be used to a limited extent When desiccation and desquamation commence the general application of vaseline containing 2 to 3 per cent phenol often relieves the intense irritation The general toxemia is combated by the usual methods employed in any severe infectious disease The diet should be nutritious with small residue and copious amounts of water should be given

As much of the toxemia and mortality is due to the secondary infection of the skin with the *Staphylococcus aureus* and other pyogenic bacteria sulfonamides and penicillin have been a great boon These should be given in full doses during the period of the eruption in the first instance as a prophylactic to the intensity of the pyogenic invasion and second to control it during the purulent stage of the eruption (see Chapter XX)

Chickenpox

Synonyms —Varicella, Glasspock '

Definition —*This is an acute specific disease which is extremely contagious and the principal sign of infection is a vesicular eruption*

Etiology —The exact cause of chickenpox is unknown It is most likely due to a filtrable virus and there has been considerable discussion as to its relation to herpes zoster, it being claimed by some that an attack of varicella protects from herpes zoster and vice versa As yet this is not proved There is some clinical evidence to suggest varicella may be contracted from persons with herpes zoster Infants are most susceptible to it It is transmitted by the droplets from the nasopharynx and by the dry crusts from the eruption It may be carried by clothing, by the hands or may be air borne



Fig 50 —Varicella in an adult (Courtesy of Dr E Wood Ruggles From Sutton and Sutton Diseases of the Skin)

Symptoms —The incubation period is about fourteen days, and the onset is acute the eruption appearing on the first day As in smallpox, a scarlatiniform or morbilliform prodromal eruption may occur The systemic symptoms are usually negligible There may be slight pyrexia and some malaise The eruption appears first as a small macule and is distinct from that of smallpox in being soft and does not have the deep seated hard papular character of the more grave disease A vesicle rapidly appears which is round or oval surrounded by a small areola and is unilocular Umbilication is not conspicuous It is easily ruptured and seldom leaves a scar as in smallpox The eruption develops in successive crops which are most numerous on those parts of the skin subject to irritation although it first appears on the face and spreads rapidly over the trunk and extremities All stages—macules vesicles and pustules—may be present at the same time

Complications —Complications of chickenpox itself are rare except secondary pyogenic infections, such as furunculosis, cellulitis, impetigo and erysipelas. Like other virus diseases, encephalitis and polioencephalitis sometimes occur Severe involvement of the mucous membranes is uncommon, but occasionally a distressing pharyngitis or laryngitis—the latter may require intubation—is met with Relapses seldom occur and second attacks are practically unknown

Pathological Anatomy —There are no characteristic anatomical changes in this disease

Diagnosis —As in smallpox, varicella is to be differentiated from other vesicular or bullous lesions, but this is comparatively easy except so far as smallpox itself is concerned A severe attack of chickenpox may closely simulate a mild attack of smallpox The description of the two eruptions would seem so distinct as hardly to suggest such confusion, but in practice this is another matter and epidemics of smallpox have been traced to such mistakes

Prognosis —The mortality from this disease is very low, and when death occurs, it can usually be attributed to secondary infections or to some other disease

Treatment —*Prophylaxis* —Isolation of all cases of chickenpox should be continued until the crusts have all disappeared and the individual has been subjected to a series of antiseptic baths All clothing bedding and utensils as well as the sickroom itself should be thoroughly disinfected In institutions convalescent serum has been used to convey a passive immunity with some success

The *active* treatment of the patient is that of any other acute infection The most important objective is preventing the child from scratching the irritating eruption as this not only aggravates the local condition but may produce secondary infections which lead to scar formation which otherwise does not occur If the eruption is not too extensive each individual lesion may be painted with equal amounts of tincture of iodine and alcohol Warm baths twice a day give great relief and are also helpful in preventing secondary infections As in smallpox the sulfonamides and penicillin are indicated to control the pyogenic infection of the eruption

Herpes Zoster

Synonyms —Shingles zoster zona

Definition —Herpes zoster is an acute infectious disease which is probably due to a filtrable virus which affects the spinal posterior root and the extramedullary cranial nerve ganglia It is characterized by a painful vesicular eruption of the skin and mucous membranes

Etiology — Although a virus has not been identified this probability is supported by the presence of intranuclear inclusions in the cells of the skin lesions and the reported experimental transmission in man The portal of entry and the way the virus reaches the ganglia are not known Furthermore the occurrence of symptomatic herpes as in malaria lobar pneumonia meningococcic meningitis etc , and its presence in association with lesions about the ganglia have never been explained

Symptoms and Signs—The onset is usually rather sudden with pain in the region of the sensory nerve distribution, malaise and fever. In three to four days an erythematous and vesicular eruption appears in these areas. Lumbar puncture usually reveals an increased cell count. In a few days the general symptoms disappear, the vesicles dry up and soon heal unless delayed by secondary infection.

Any one or more of the spinal ganglia may be and are most commonly involved. Although any of the cranial nerves may be affected, it is rare except for the first branch of the sensory division of the trigeminal nerve. This may lead to corneal ulceration, which is serious and requires expert ophthalmic attention.

Prognosis—This is always good and complete recovery is the rule. Pain over the area of eruption may persist for many weeks and even months, particularly in elderly people. It may be most troublesome and very refractory. There is rarely a residual paralysis.

Diagnosis—This is divisible into the preeruptive and posteruptive phases. In the former, pain is the outstanding feature and may be confused with pericarditis, coronary occlusion, plastic pleurisy, cholecystitis, appendicitis or other acute visceral lesion. When the eruption appears, the diagnosis is quite clear. There are, however, cases in children and occasionally in adults where numerous vesicles unrelated to the nerve distribution appear and closely simulate varicella. In fact, as mentioned on page 1399, there is clinical and epidemiological evidence which would indicate that the viruses of these two diseases are closely related.

Treatment—There is no specific cure for this disease. Therefore, as would be expected, all and sundry remedies have been advocated on scant evidence and with no consistent success. The prolonged pain may be so disturbing as to require posterior root section or ganglionectomy.

Lymphocytic Choriomeningitis

Definition—This is an acute infectious disease with mild influenza-like prodromata followed in some instances by acute lymphocytic meningitis. It is due to a filtrable virus and has a wide distribution in North America, Europe and Asia.

Etiology—The virus is of medium size and affects many laboratory animals as well as man. The method of transmission is not known, but certain blood-sucking insects have been shown to transmit the virus experimentally. Therefore there may be several avenues of infection.

Symptoms and Signs—The incubation period is a few days. The first period is characterized by general malaise, pains in limbs, headache, slight prostration and moderate fever with a leucopenia. There may also be a sore throat and cough. This phase lasts for a few days to several weeks with gradual improvement and the fever disappears. After a lapse of one or two days it returns with the signs of meningeal irritation—headache, drowsiness, nausea, vomiting, stiffness of the neck and Kernig's sign. The leucopenia has now disappeared. The spinal fluid shows increased pressure and a lymphocytosis of 100 to 1,000 or more per cu mm, with increased protein and nor

Complications—Complications of chickenpox itself are rare except secondary pyogenic infections, such as furunculosis, cellulitis, impetigo and erysipelas. Like other virus diseases, encephalitis and polioencephalitis sometimes occur Severe involvement of the mucous membranes is uncommon, but occasionally a distressing pharyngitis or laryngitis—the latter may require intubation—is met with Relapses seldom occur and second attacks are practically unknown

Pathological Anatomy—There are no characteristic anatomical changes in this disease

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Prognosis—The mortality from this disease is very low, and when death occurs, it can usually be attributed to secondary infections or to some other disease

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Etiology—Although a virus has not been identified this probability is supported by the presence of intranuclear inclusions in the cells of the skin lesions and the reported experimental transmission in man The portal of entry and the way the virus reaches the ganglia are not known Furthermore the occurrence of symptomatic herpes as in malaria lobar pneumonia meningococcic meningitis etc and its presence in association with lesions about the ganglia have never been explained

Diagnosis—The diagnosis rests upon the adenopathy, splenomegaly, pyrexia and mononuclear leucocytosis It is to be differentiated from other diseases such as German measles which present a somewhat similar clinical pattern and from acute lymphocytic meningitis A 'heterophile antibody reaction' (agglutination of sheep's red cells) has been found in the disease (85 per cent) and has been used in diagnosis It is not absolutely specific

Treatment—The treatment is nonspecific and consists of rest in bed and other procedures indicated in any infectious disease

Epidemic Pleurodynia

Synonyms—Myalgia epidemica epidemic transient diaphragmatic spasm, epidemic diaphragmatic pleurodynia Devil's grip Bornholm's disease

Definition—Epidemic pleurodynia is a highly infectious and contagious disease characterized by intense paroxysmal pain in the upper abdomen and lower thorax in the region of the diaphragmatic attachment There is also pyrexia and headache

Etiology—It is a definitely epidemic disease and has been reported from many countries particularly Iceland Finland Scandinavia the Mid Atlantic States, and Ohio Illinois and Indiana It is most prevalent during the summer months and over 50 per cent of the cases in epidemics occur in children under fifteen years The exact cause is not definitely known but some evidence suggests it to be a filtrable virus The portal of entry is supposed to be through the nasopharynx and it is transmitted by direct contact There is no evidence to indicate that it is carried in food drink or by insects

Symptoms and Signs—There are no prodomata and the onset is sudden with pain in the upper epigastrium and lower anterior thorax This may vary in intensity from a dull ache or distress to the most exquisite agony particularly in paroxysms It is intimately associated with the diaphragmatic insertions and is always aggravated by increased respiratory movement as in deep breathing coughing sneezing or laughing Although this symptom is the most conspicuous pain tenderness hyperesthesia and muscular rigidity in other areas may also be detected indicating systemic dissemination of the virus With the pain there is also rapid pyrexia reaching 104° F in a few hours Chills occur in about half the cases The fever lasts for 24 to 48 hours when the temperature usually returns to normal but this is frequently followed by a recrudescence of both pain and fever It may run an irregular course for ten to fourteen days Other symptoms are headache (sometimes intense) prostration while nausea vomiting diarrhea, and tympanitis are particularly common in children The respirations are shallow and the severe pain may embarrass pulmonary function and lead to cyanosis

Physical examination sometimes reveals a pleural friction rub The epigastrium is tender on deep palpation and the lower thorax may be quite sensitive The leucocyte count may vary from four to twenty five thousand although it is usually within normal limits A definite eosinophilia, up to 15 per cent may be found during convalescence

The principal visceral lesions which may be considered as complications are fibrinous pleuritis fibrinous pericarditis orchitis and rarely jaundice

and sugar content. This phase lasts a week to ten days with gradual recovery, although the spinal fluid findings lag behind the clinical signs.

In addition to the meningeal involvement the only other system commonly affected is the respiratory. A bronchitis and bronchopneumonia are not uncommon in the more severe cases and would appear to be an important factor in the few cases in man with a fatal termination.

Pathology.—There have been very few autopsies in man. In one case with a fatal ending, apparently due to an unusually virulent virus, an interstitial bronchopneumonia was the most prominent feature. In a more chronic case the choroid plexus, ventricular walls and meninges showed marked thickening and infiltration, and absence of the arachnoid space over the basal area.

Prognosis.—This is good, as the death rate is almost negligible and sequelae are unknown except for the very occasional hydrocephalus in children.

Treatment is entirely symptomatic.

Acute Mononucleosis

Synonym.—Glandular fever.

Definition.—This is an acute infectious disease with pyrexia, superficial adenopathy, and a mononuclear leucocytosis.

Etiology.—There is considerable doubt as to whether this is a specific disease or whether it may not comprise a group of unknown infections, as undoubtedly other diseases with a lymphocytosis such as German measles are sometimes confused with it. The cause is unknown, although in recent years there have been an increasing number of cases reported in which the *Listerella monocytogenes* has been isolated either from the peripheral blood or from the cerebrospinal fluid. In time such cases may crystallize into a specific disease.

Symptoms.—The onset of the disease is insidious with pyrexia, pharyngitis or tonsillitis, headache, chills, abdominal pain and sweating. The temperature is irregular and gradually reaches 100° to 101° F. On physical examination the cervical lymph nodes are first enlarged and tender. This is followed by a similar general adenopathy with enlargement of the tonsils, and splenomegaly. The tonsils are painful and occasionally definite follicular, lacunar, or membranous tonsillitis occurs. The outstanding feature of the disease is the great increase in the mononuclear leucocytes in the circulating blood. They may number as many as 30,000 per cu. mm. and there is not only a relative but an absolute reduction in the granulocytes. There has been some discussion as to whether the mononuclear cells are monocytes, and in many instances there is no doubt that they are lymphocytes. In those cases identified with *Listerella monocytogenes* large numbers of monocytes are found, and it is not unusual for these patients to develop meningeal symptoms and a so-called lymphocytic meningitis may be present. This listerella has been isolated from the spinal fluid of some of these cases.

The *anatomical changes* are not specific, the lymph nodes alone showing considerable hyperplasia. The *course* of the disease is invariably to recovery. The pyrexia lasts from two to three weeks.

Diagnosis —The diagnosis rests upon the adenopathy, splenomegaly, pyrexia and mononuclear leucocytosis It is to be differentiated from other diseases such as German measles which present a somewhat similar clinical pattern and from acute lymphocytic meningitis A "heterophile antibody reaction" (agglutination of sheep's red cells) has been found in the disease (80 per cent) and has been used in diagnosis It is not absolutely specific

Treatment —The treatment is nonspecific and consists of rest in bed and other procedures indicated in any infectious disease

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Etiology —It is a definitely epidemic disease and has been reported from many countries particularly Iceland, Finland, Scandinavia, the Mid Atlantic States, and Ohio Illinois and Indiana It is most prevalent during the summer months and over 50 per cent of the cases in epidemics occur in children under fifteen years The exact cause is not definitely known but some evidence suggests it to be a filtrable virus The portal of entry is supposed to be through the nasopharynx and it is transmitted by direct contact There is no evidence to indicate that it is carried in food, drink or by insects

Symptoms and Signs —There are no prodomata and the onset is sudden with pain in the upper epigastrium and lower anterior thorax This may vary in intensity from a dull ache or distress to the most exquisite agony particularly in paroxysms It is intimately associated with the diaphragmatic insertions and is always aggravated by increased respiratory movement as in deep breathing coughing sneezing or laughing Although this symptom is the most conspicuous pain tenderness hyperesthesia and muscular rigidity in other areas may also be detected indicating systemic dissemination of the virus With the pain there is also rapid pyrexia reaching 104° F in a few hours Chills occur in about half the cases The fever lasts for 24 to 48 hours when the temperature usually returns to normal but this is frequently followed by a recrudescence of both pain and fever It may run an irregular course for ten to fourteen days Other symptoms are headache (sometimes intense) prostration while nausea vomiting diarrhea and tympanitis are particularly common in children The respirations are shallow and the severe pain may embarrass pulmonary function and lead to cyanosis

Physical examination sometimes reveals a pleural friction rub The epigastrium is tender on deep palpation and the lower thorax may be quite sensitive The leucocyte count may vary from four to twenty five thousand, although it is usually within normal limits A definite eosinophilia up to 15 per cent may be found during convalescence

The principal visceral lesions which may be considered as complications are fibrinous pleuritis fibrinous pericarditis orchitis and rarely jaundice

mal sugar content This phase lasts a week to ten days with gradual recovery although the spinal fluid findings lag behind the clinical signs

In addition to the meningeal involvement the *only* other system commonly affected is the respiratory A bronchitis and bronchopneumonia are not uncommon in the more severe cases and would appear to be an important factor in the few cases in man with a fatal termination

Pathology —There have been very few autopsies in man In one case with a fatal ending apparently due to an unusually virulent virus an interstitial bronchopneumonia was the most prominent feature In a more chronic case the choroid plexus ventricular walls and meninges showed marked thickening and infiltration and absence of the arachnoid space over the basal area

Prognosis —This is good as the death rate is almost negligible and sequelae are unknown except for the very occasional hydrocephalus in children

Treatment is entirely symptomatic

Acute Mononucleosis

Synonym —Glandular fever

Definition —This is an acute infectious disease with pyrexia, superficial adenopathy, and a mononuclear leucocytosis

Etiology —There is considerable doubt as to whether this is a specific disease or whether it may not comprise a group of unknown infections as undoubtedly other diseases with a lymphocytosis such as German measles are sometimes confused with it The cause is unknown although in recent years there have been an increasing number of cases reported in which the *Listerella monocytogenes* has been isolated either from the peripheral blood or from the cerebrospinal fluid In time such cases may crystallize into a specific disease

Symptoms —The onset of the disease is insidious with pyrexia pharyngitis or tonsillitis headache chills abdominal pain and sweating The temperature is irregular and gradually reaches 100° to 104° F On physical examination the cervical lymph nodes are first enlarged and tender This is followed by a similar general adenopathy with enlargement of the tonsils and splenomegaly The tonsils are painful and occasionally definite follicular lacunar or membranous tonsillitis occurs The outstanding feature of the disease is the great increase in the mononuclear leucocytes in the circulating blood They may number as many as 30 000 per cu mm and there is not only a relative but an absolute reduction in the granulocytes There has been some discussion as to whether the mononuclear cells are monocytes and in many instances there is no doubt that they are lymphocytes In those cases identified with *Listerella monocytogenes* large numbers of monocytes are found and it is not unusual for these patients to develop meningeal symptoms and a so called lymphocytic meningitis may be present This listerella has been isolated from the spinal fluid of some of these cases

The *anatomical changes* are not specific the lymph nodes alone showing considerable hyperplasia The *course* of the disease is invariably to recovery The pyrexia lasts from two to three weeks

seldom occurs in infants children are not uncommonly infected, but it most frequently develops between the ages of twenty and fifty, and more often in the male than the female Heredity plays no role in its transmission

Symptoms —The exact incubation period is unknown and its life history is probably almost identical with that of tuberculosis although acute cases



Fig 06 —Nodular leprosy (Courtesy of Dr Howard Morrow From Sutton and Sutton Diseases of the Skin)



Fig 0 —Tubercular leprosy (Photograph by Bureau of Science Manila Dr John A Johnston Acting Director From Sutton and Sutton Diseases of the Skin)

are rare When fully developed the disease is localized most frequently to the skin and mucous membranes or to the nervous system In some the former predominate and in others the latter but in practically all cases there is some involvement of both Therefore three principal varieties have been

Such lesions as sinusitis, otitis media, pyelitis, and bronchopneumonia, are most probably due to secondary infections

The **pathological anatomy** of this disease has never been explored as there have been no autopsies recorded Abdominal laparotomies have been done through mistaken diagnoses but no abnormal findings have been detected

The **diagnosis** seldom offers any difficulty in epidemics but, in sporadic cases and in the initial stages of an outbreak this disease is often mistaken for acute peritonitis of the upper abdomen due to perforated peptic ulcer cholecystitis, acute pancreatitis, etc It is further confusing in children with pronounced gastrointestinal symptoms The intensity and paroxysmal character of the symptoms with fever and headache should suggest the proper diagnosis Other diseases with which it may be confused are acute diaphragmatic pleurisy (pneumonococcic, rheumatic or tuberculous) herpes zoster dengue etc Each has its characteristic features, however

The **course** of epidemic pleurodynia may vary considerably from a mild, comparatively painless, two days' illness to the most exquisite agony Recurrences are common and the disease may be prolonged by these for several weeks The death rate is insignificant, only about a dozen deaths having been recorded in tens of thousands of cases

Treatment —This is purely symptomatic Bed rest sedatives, analgesics and strapping the lower thorax and epigastrium to restrict diaphragmatic and intercostal movements offer the best means of making less uncomfortable this painful but not serious disease

Leprosy

Definition —Leprosy is a specific chronic infectious disease caused by the *Mycobacterium leprae* or *B leprae* It has a particular predilection for the mucocutaneous tissues and the peripheral nerves

Distribution —In former centuries leprosy was not only a disease of wide distribution but of high incidence Partly through persistent and compulsory, although unorganized isolation it has greatly diminished in frequency, although there is probably no country in the world where it has been completely eradicated It is most common in eastern and southern Asia, the islands of the Pacific and Australasia In the Western Hemisphere it is most common in the West Indies Mexico, Central America and the southern countries of South America In the United States and Canada sporadic cases are seen and in addition there are definite foci in Louisiana Minnesota California, and South Carolina

Etiology —The disease is considered to be due to *Myco leprae* which is closely related to the tubercle bacillus both in its staining and cultural characters It can always be recovered from the typical anatomical lesions although as yet the disease has not been artificially transmitted to man or the lower animals The method of its transmission is also in doubt The frequency with which the initial lesions are found in the mucous membrane of the nose suggests that it may gain entrance through the nasal mucous membrane It

smooth and often have the texture of velvet They are most noticeable on the face, the hands and the feet, about the genital region, and over the lower abdomen and inner sides of the thighs The pigment of the skin gradually fades and becomes a fawn color Some of the nodules entirely disappear while others progress in a centrifugal manner until large areas of the skin are involved The thickening of the skin of the face spreads over the nose cheeks the eyebrows—the hair on the outer half of which is lost—about the mouth and into the lobes of the ears, giving to the individual a peculiar mask like or "leonine" appearance The skin becomes dry and ichthyotic and *sometimes looks like pigskin with the hair follicles open and prominent* The nails are filtrated at their bases and may become striated and malformed Successive crops of the primary erythematous and nodular lesions may involve any part of the skin Whereas at first they are reddish brown or of a violaceous hue, they soon fade to the dusky brown color described above While this is the usual course of the lesions ulceration with loss of tissue also occurs There may be great destruction of the bones of the nose pharynx, and larynx with perforation of the palate The eyes are not infrequently involved leading to keratitis iridocyclitis and even blindness These destructive lesions may show healing in some portions, and extension in others The scar tissue resulting leads to great deformity which not only involves the skin but also the mucous membrane of the pharynx and larynx Peripheral lesions of the fingers and toes may involve the cutaneous and deeper tissue with local necrosis loss of substance and absorption of the fingers and toes induced by the trophic effects due to the peripheral nerve lesions

Neural or Anesthetic Leprosy—In addition to extensive and more or less symmetrical cutaneous lesions, there is a definite evidence of neural involvement The skin lesions in their early stages are erythematous and may simulate erythema multiforme but in time the skin becomes smooth and brownish with a clear cut margin Vesiculation and superficial ulceration is uncommon

At first these areas are irritable and hyperesthetic but as time passes they gradually become less so and anesthesia follows This is parallel to the involvement of the peripheral nerve trunks particularly the ulnar, tibial posterior cervical and peroneal On palpation they will be found thickened and nodular and pressure on them elicits no pain In addition to the anesthesia there is an absence of the sense of touch and of heat and cold Therefore the part is particularly liable to trauma and burns as in syringomyelia which may lead to extensive ulceration and necrosis The trophic changes in the skin and muscles now become prominent the thenar and hyperthenar eminences become flattened and the interosseous spaces pronounced from wasting muscles There are contractures which are most obvious in the upper extremities producing the so called claw or leper hand The atrophy of the face muscles still further accentuates the mask like appearance already mentioned

Pathological Anatomy—The essential anatomical lesion of leprosy is a granuloma and in this way closely approximates the more chronic lesions of the tubercle bacillus and *Treponema pallidum* In fact it is sometimes difficult to be certain of their histological differentiation The lesion contains

described, the mucocutaneous or nodular type, the neural or anesthetic type, and the mixed type The last is an unnecessary division and only leads to confusion

The earliest symptoms are vague and are usually those of any chronic insidious infection, namely, general malaise, headache, debility and various muscular and neuritic pains Occasionally bouts of pyrexia may be recorded, while rhinitis is quite common and further suggests that the portal of entry



Fig 508 —Photograph of a case of leprosy showing pronounced thickening of the skin of the face and ears (Courtesy of Dr J L Todd)

may be through the nasal mucous membrane In time the true characteristics of the disease begin to manifest themselves and these may be divided for the sake of simplicity into those of the two major symptom patterns

Mucocutaneous or Nodular or Tubercular Leprosy—The characteristic lesions are nodular or tubercular They appear on the skin as reddish brown spots varying from one quarter to several inches in diameter They are seldom much elevated, but give the impression that the skin is thickened but are

drops, three times daily, in any vehicle which the patient may desire, and must be continued over long periods In some unfortunates it causes gastric irritation which prevents its use It may be administered by intramuscular injections This is usually prepared according to the "Mercado" formula which is chaulmoogra oil and camphor 60 cc each and resorcin 4 grams 0 3 cc to 3 cc injected intramuscularly two or three times a week Unfortunately this usually produces local pain More recently the fatty acids of chaulmoogra oil have been employed, and also the ethyl esters of the fatty acids These may also be injected intramuscularly, while other combinations have been advised also The treatment must be continued for several years at least although short periods of intermission may be allowed As in other infections, the earlier treatment is started in the disease the more gratifying are the results

Recently promin (sodium p p′ diaminodiphenylsulfone N N didextrose sulfonate) and diasone (disodium formaldehyde sulfoxylate diaminodiphenyl sulfone) have given encouraging results but still require prolonged clinical trials The former is given intravenously in doses of 2 to 5 Gm daily in courses of two weeks with a week s interval The latter may be given by mouth in 0 3 Gm capsules two to three times a day with meals There should also be a few days rest period every 4 to 6 weeks

The cutaneous lesions respond quite favorably to x ray therapy, while radium has more recently been employed in lesions of the mouth and eye Local aseptic measures should be used until the ulcerated areas are healed and sometimes surgical procedures are indicated The patient should be kept in a cheerful community, and with modern treatment hope should be the watchword The general handling of the case is similar to that of tuberculosis

Toxoplasmosis

Toxoplasmosis is a recently recognized infection due to the genus *Toxoplasma* The organisms have been recovered from body exudates and fluids but usually are intracellular singly or in clumps in nerve muscle and endothelial cells and in mononuclear polymorphonuclear eosinophile and epithelioid cells They are minute (2 5 by 1 5 2 microns) pleomorphic (rounded oval crescentic pyriform or elongated) protoplasmic masses

The portal of entry is not known It is accepted however that it can be an intrauterine infection Under such conditions the principal locus of involvement is the central nervous system In the postpartum infection the organs involved are usually the lungs the kidneys and the skin

The pathological process is first in the blood vessels causing an acute arteritis and phlebitis with rapid necrosis and involvement of surrounding tissue with the eventual formation of a granuloma proceeding to calcification The clinical pattern will depend upon the localization of these lesions In the prenatal cases there are signs of advanced encephalitis and hydrocephalus In the postnatal cases there is pneumonitis necrotic glomerulonephritis and an exanthem resembling that of typhus Splenomegaly and hepatomegaly with icterus have also been reported

many epithelioid cells, vacuolated giant cells, connective tissue cells, mast cells lymphocytes, and plasma cells There is also a characteristic large, ovoid cell which is called the "lepro cell," the exact significance of which is not yet settled The granulomatous processes may lead to great destruction of tissue It is commonly serpiginous, leaving distortion with contracting scar tissue

Diagnosis—The advanced cases must be differentiated from tuberculosis, syphilis blastomycotic disease and in some cases from leucemic infiltration with ulceration This can be readily accomplished either by biopsy of the infected tissue or direct detection of the *Myco lepiae* in smears, especially from the nasal mucous membrane In the early stages and particularly in endemic cases, the diagnosis may be attended by some difficulty There are, however a number of points which when taken together are of great aid These are the peculiar fawn or yellowish brown color of the skin which may be either hyperesthetic or anesthetic, and in particular the involvement of the lobes of the ears and the eyebrows, with alopecia of the outer half of the latter The various skin eruptions may be simulated by syphilis, and unfortunately for the differential diagnosis, the Wassermann reaction is frequently positive in nonsyphilitic lepers Syringomyelia is the principal disease to be eliminated in the purely neural type

Prognosis—Until the last generation leprosy was looked upon as a hopeless disease but recent advances in its therapy have changed this from gloom to hope The disease is chronic and may extend over many years but eventually the mutilating deformities make the patient a piteous sight Fortunately not all are so afflicted and may live to an advanced age without distress or tissue destruction dying of some entirely different disease

Treatment—*Prophylaxis*—The nasal and nasopharyngeal discharges, and the exudate from cutaneous ulcerating lesions harbor the virus of this disease Therefore such materials and articles which they may contaminate should be destroyed It is best that patients with open lesions be segregated, and this has been done in many countries where they are housed at government expense in leper colonies Such isolation has undoubtedly been an important if not primary factor in the localization of this disease and the great decline of its incidence Its similarity to tuberculosis would suggest that this would be a proper method to control this latter disease and in fact this has been successfully demonstrated in many areas but the accomplishment of these public health measures in tuberculosis has not been assisted by the same fear of the disease the outcast" and the ' unclean ' being synonyms of the leper from biblical times

The neural type without nasal or nasopharyngeal ulceration may be looked upon as ' closed cases but before they are allowed to mingle in society it should be clearly demonstrated that *Myco lepiae* are not present in the nasal secretions even though no macroscopic lesion is evident but to be on the side of safety these cases should also be quarantined until the urine and feces have been thoroughly examined as it is well known that they may contain the bacilli

The *active* treatment of leprosy rests principally upon the use of chaulmoogra oil and its derivatives The pure oil may be given by mouth *5 to 60*

legs and forearms They are extremely painful and tender and soon assume a purplish and then a yellowish color before they disappear after a period of several days or weeks They may recur in crops They were at one time identified with rheumatic fever (see page 67) but in recent years have also been considered as an allergic evidence of primary tuberculosis Although most frequently associated with these two diseases they have also been found with nonspecific streptococcal infections with syphilis and with other organisms It cannot be considered as a specific lesion but rather as an allergic reaction most frequently indicative of the first two diseases

ERYTHEMA MULTIFORME.—Obviously a most diverse type of erythema which not only assumes many and varied characteristics but appears both on the skin and mucous membranes Its cause is unknown although the prevalent ideas of focal infections and intestinal intoxications have held a popular place It may simulate syphilis ringworm pemphigus pityriasis, lupus erythematosus etc In fact it is a protean sign of multitudinous etiologies and not a specific disease

Lupus Erythematosus Disseminatus

Synonyms—Ulerythema centrifugum Seborrhea congestiva

Definition—Lupus erythematosus is a systemic disease characterized at some time in its course by an erythematous eruption usually on the face and scalp There are also various vascular and other visceral lesions which indicate its systemic character It has not been proved as tuberculous, and it is unfortunate that the term "lupus" has been identified with it as it is quite distinct from "lupus vulgaris"

Etiology—Some claim that it is due to tuberculosis while others name the streptococcus This is a fairly common claim for a number of diseases (see Erythema nodosum) There is one important factor in its etiology which must be emphasized namely that sunlight or ultraviolet light seem at times to initiate the disease Females in the third and fourth decades are principally affected and males seldom

Symptoms and Signs—The onset is most irregular as almost any of the features to be described below may first cause the patient to seek medical advice In spite of the bizarre and irregular manifestations the true diagnosis may be arrived at before the typical skin lesions appear These however may be transitory or long delayed leading to continued confusion

The onset may be either insidious or explosive and there may be a preceding history of Raynaud s disease like lesions in the fingers With the insidious onset there is fatigue and exhaustion low fever and joint pains which may lead to confusion with rheumatoid arthritis or rheumatic fever In time the skin lesions may appear or be preceded by signs of visceral disease With the acute onset the constitutional and skin lesions may appear together with high fever and great prostration

Skin Lesions—The most characteristic lesion is a symmetrical dermatitis over the nose and cheeks with edema of the eyelids The lesions may appear elsewhere as bright reddish violet papillary or bulbous with petechiae or purpura With involution there may be pigmentation similar to that of Ad

The neurologic signs are quite diverse, including those of internal hydrocephalus, bilateral chorioretinitis, hyperactive reflexes, Babinski's sign, spastic contractures, nystagmus and convulsions. In survivors there is impaired vision and defective mental development. The spinal fluid is xanthochromic with a cellular content of 1,000 or more, chiefly lymphocytes. The clue to the exact diagnosis is found through the x-ray revealing the calcified granulomata.

Although the **prognosis** is always grave as to life and future disabilities, there are undoubtedly asymptomatic cases recognized accidentally by x-ray or at postmortem. There has now been developed by Warren and Sabin a complement fixation test which is most helpful in the early stages of the disease if it be suspected.

The treatment is symptomatic for the present, although certain of the sulfonamides may be helpful.

ERYTHEMATOSES

Erythema is due to dilatation of the superficial capillaries and appears either in localized areas or as a general phenomenon, as in scarlet fever. It would not properly be included in a text on internal medicine if it did not present the principal evidence in a group of little understood but apparently systemic diseases. On the other hand, erythema is simply a sign which in the older nosography was sometimes elevated to a position of a specific disease. With our present day method of analyzing cause and effect and making diagnoses from factual evidence, erythema becomes a sign, as do purpura and many other dermatological manifestations. It has frequently associated with it swelling or edema, heat, itching, tenderness and pain, but these are not necessarily present; thus erythema serves as a lead in diagnosis rather than as an entity unto itself. It would seem that the time has arrived when the skin manifestations of systemic disease should be described even in a single volume as they comprise a large and important realm of medicine and would undoubtedly contribute to a better understanding of the physiology and pathology of both.

The erythemas are often of importance as they may be symptomatic of some external or internal cause. The former are usually contact irritations such as nettles, poison ivy, heat, pressure, x-rays, turpentine, mustard, cantharides, etc. The internal cause is ingestion or inhalation of a wide variety of substances to which the person may be allergic (see page 1441). In addition there are certain drugs which may give a similar reaction; the following are the more important—atropine, belladonna, quinine, salicylates, chloral, barbiturates, sulfanilamide and its derivatives, etc. The first two give an erythema on account of a specific pharmacological effect, while in the rest the effect is due to an idiosyncrasy and is usually called "erythema medicamentosum," and may produce a multitude of other skin manifestations.

In addition, there are a few types of erythema which would seem to have a more specific systemic indication.

Erythema Nodosum.—This is a rather specific type of lesion characterized by circumscribed indurated erythematous areas on the extensor surfaces of the

but numerous thromboses A false positive Wassermann reaction is frequently found *Enlargements of the spleen and liver are usual findings* and thrombotic necrosis of the former has been recorded

Cardiovascular System—The vascular lesions which have been recorded with increasing frequency as an important visceral feature of this disease may be the essential clue to its real pathological anatomy including the skin There may be ischemic lesions of the fingers and toes resembling Raynaud s disease (see page 464) But these vascular lesions are more characteristic in the kidneys where the glomerular tufts are *principally* involved It has been difficult to be certain as to the nature of these lesions but the usual appearance is that *of hyalinization of the arterioles and round celled infiltration about them* This often leads to renal failure with the usual urinary and blood chemistry findings There is sometimes hypertension with cardiac hypertrophy which may be independent of a verrucose endocarditis with mitral and aortic insufficiency The endocarditis (Libman Sachs) is not clinically specific but occurs too often to be a coincidental lesion Vascular lesions are also found in the retina in the form of small hemorrhages and exudate independent of renal lesions and hypertension There may also be focal vascular changes in the central nervous system which may produce a variety of clinical signs Purpura and a Rumpel Leede reaction are common In addition to these disseminated vascular lesions involvement of the serous membranes especially pleuritis and pericarditis is frequently encountered These may pass through the complete cycle of serous inflammation from fibrinous exudate to effusion

Pathology—The pathological features of this disease are chiefly in the histological findings It may be taken as an example of the so called '*collagen diseases* in which group can be included scleroderma dermatomyositis and periarteritis nodosa In fact some pathologists would also include as allied diseases rheumatic fever rheumatoid arthritis and malignant nephrosclerosis

The typical lesion is found in the small blood vessels throughout the body but principally in those of the kidneys heart lungs liver and serous membranes There may be little macroscopical evidence of this but microscopically there is fibrinoid degeneration of the collagen or fibrous connective tissue which is characterized by straightening and thickening of the collagen fibers increased friability a smudgy eosinophilic staining and increase of the ground substance There is also a cellular infiltration surrounding the vessels and finally fibrosis leading to thrombosis and obliteration of the lumen with at times rupture of the vessels

Diagnosis—This is most difficult without the skin lesions to point to the truth and even these may be confusing A biopsy of the skin may help but even with this aid it may be difficult to differentiate from scleroderma dermatomyositis and periarteritis nodosa It may be confused with rheumatic fever rheumatoid arthritis subacute bacterial endocarditis acute and chronic nephritis essential hypertension granulocytopenia and a number of other visceral lesions

Prognosis—The course of the disease is proverbially uncertain The arthralgia pyrexia and general debility may long antedate the skin lesions

dison's disease These lesions appear chiefly on the exposed surfaces The finger tips are often first involved but they may be found also on the torso

There have been described three varieties (1) symmetrical erythema, (2) local atrophic erythematosus, (3) exanthematous erythematosus The first and third are probably identical and their distinction is artificial in relation to the systemic quality of the disease It is not within our present province to enter into the discussion as to whether atrophy of the skin is essential to distinguish these lesions because the significance of the skin lesions is to give a lead to the internist as to the systemic disease with which he has to deal

SYSTEMIC FEATURES —The onset may coincide with an acute pharyngeal infection or may be preceded by a moderate to severe sunburn In fact with the present popular use of ultraviolet rays some cases may date from its use It is difficult to correlate these physical agents with the initiation of the visceral lesions



Fig 509 —Lupus erythematosus (seborrheic type) (Courtesy of Dr Grover W Wende From Sutton and Sutton Diseases of the Skin)

Arthralgia or *exudative arthritis* with myalgia and vague pains is common not only as an initial complaint but also during the course of the disease Indeed acute rheumatic fever may be the diagnosis for many months and the condition may be treated accordingly particularly is this the case when endocarditis and serous membrane lesions develop (see below)

The findings in the *blood* are most interesting There is usually a leucopenia, which may be quite alarming when as low as 1 000 per c mm This however, is not constant as a moderate leucocytosis has been recorded, but this is usually associated with a secondary infection Anemia is sometimes conspicuous but is not at all distinctive Thrombocytopenia has frequently been reported and it has been suggested that this is not primary but is secondary to the vascular lesions in which the thrombocytes are entrapped leading to minute

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when a positive diagnosis may be made After this there may be repeated remissions or it may run its course in a few months The terminal stages are usually characterized by bronchopneumonia but other cases may develop a nonspecific toxemia cerebral signs circulatory failure, or renal failure

Treatment—This is highly ineffective although bismuth has been advocated At least it seems to do no harm, which is more than can be said for gold therapy x ray, sunlight and ultraviolet therapy, all of which are strictly prohibited Until the cause and pathogenic pattern of this disease are known speculative therapy may do more harm than good Cautious general symptomatic therapy is therefore the best course to pursue

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CHAPTER XX

CHEMOTHERAPY AND ANTIBIOTICS

Definition.—For nearly one hundred years it has been an ambition of pharmacologists to produce chemical agents which would have a bactericidal or bacteriostatic influence on specific organisms pathogenic to man and to domestic animals. Primitive examples are found in mercury as a spirocheticide in syphilis before the *Treponema pallidum* was discovered, ipecacuanha was used for *amebiasis* long before emetine was found to be a relative specific and quinine was known to be an almost certain antagonist to the *Plasmodium malariae*. These are but a few examples of the shrewd therapeutics of history to which might be added the physiological and nutritional empiricisms such as digitalis in cardiac failure and citrus juices and even slippery elm as an antidote to scurvy. Many of man's hopes for the prevention and antagonism to disease or abnormal states have been rewarded by spectacular successes. In addition to the above there are the triumphs of substitution therapy as in the combat against hypothyroidism, diabetes, pernicious anemia, Addison's disease, etc. In all of these and other diseases including infections, food and organismal deficiencies, there has been the ambition to seek a specific cure or remedy, and to a great degree this has been successful.

When one considers the infectious diseases in their broadest scope, the noxious agents have been so many and diverse in a biological sense including filtrable viruses, rickettsia, bacteria, spirochetae, spirilla, plasmodia, protozoa, etc., that the range for specific remedies would seem almost infinite. But still the quest goes on by determined effort, consummate patience, and courage with real hazards as has been shown by the number who have fallen by the agents of the diseases that they were striving to conquer.

It has long been known that products of certain bacteria, molds, and other lower forms of life were beneficial or helpful in the growth of others of the same, higher or lower species. These became known as *biotic* substances. It was also known that there were produced, on the contrary, substances that were antagonistic to the growth and survival of these same and other species. These were known as *antibiotics*. There are many of these which have been successfully demonstrated in vitro but have been found to be too toxic for use in laboratory animals and finally impracticable in man. Therefore the range of *antibiotics* in the combat against human diseases has been limited in number but fortunately not in the variety of bacteria and other organisms which are causative of diseases.

The chemotherapeutic agents and antibiotic substances have a common purpose and general action. Therefore it would be profitable and proper to discuss them both under a common designation.

The number of chemotherapeutic agents are rather numerous when we consider the arsenicals, bismuth, mercury, quinine, atabrine, emetine, anti-

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mony salts etc But in this chapter there will be considered only the sulfonamides and the antibiotics—penicillin streptomycin etc

In 1935 when Domagk published his experiments showing that 4′ sulfamido 2 4 diamino azo benzene had a spectacular effect on hemolytic streptococcal infections in mice a new era in chemotherapy was born A few months later the Trefouels and associates pointed out that para aminobenzenesulfonamide was apparently the active part of the compound with which Domagk had worked There soon followed many clinical reports of the value of the original compound and its soluble derivative the disodium salt of 4 sulfamide phenyl 2 azo 7 acetylamino 1 hydroxy naphthalene 3 6 disulphonic acid Much confusion was created by the number of trade names given to this compound some of which were prontosil prontylin streptamid, streptocide colsulanyde and prontosil album It was suggested to the Council of Pharmacy and Chemistry that the nonproprietary name of "sulfanilamide" should be adopted This was accepted as it denoted the composition and was also being used abroad Since then other compounds have been brought into use such as sulfapyridine sulfathiazole sulfadiazine and sulfaguanidine On account of the number of these compounds and the prospect of still others the inclusive name of "sulfonamides has been adopted to indicate these forms of chemotherapeutic agents in general

In 1929 Fleming published an account of an active agent obtained from a certain type of Penicillium which had a powerful bacteriostatic action on certain pyogenic cocci It was given the name of penicillin Further work revealed that this agent could be found in the filtrate of broth cultures of the *Penicillium notatum*

In 1942 Florey and Jennings established a unitage for this substance This is known as the Oxford unit It is the amount of *penicillin* which when dissolved in 50 c c of meat extract broth just inhibits completely the growth of a test strain of *Staphylococcus aureus* The work of Fleming and its confirmation by Florey stimulated anew the search for antibiotics that could be used in man Several scores of antibiotic substances have so far been produced but of all these *streptomycin streptothricin aureomycin* and *chloromycetin* are the only ones in addition to *penicillin* that have been found to be sufficiently nontoxic to have a therapeutic value in man *Streptothricin* is produced by the growth of *Streptomyces lavendulae streptomycin* from *Streptomyces griseus* and *aureomycin* from *Streptomyces aureofaciens* To the present the reports on the clinical use of streptothricin have been few It has been found both in vitro and in vivo in experimental animals to be effective against gram negative bacteria In fact streptothricin and streptomycin have almost identical therapeutic effects but a much greater amount of clinical work has been done with streptomycin The streptomycin unit (S U) is the amount of material that will inhibit the growth of *E sch coli* in 1 c c of medium equivalent to 1 mg of streptomycin base

Bacterial Effect — The action of sulfonamides and antibiotics upon bacteria is in most part bacteriostatic although they may have variable bactericidal actions These effects in the main therefore prevent the multiplication of the organisms within the tissues and tissue fluids permitting their destruc

important effect upon the intestinal bacteria and consequently is particularly efficacious in such dysenteric infections. It has been used with good effects in intestinal and particularly colonic operations. Sulfanilamide on account of its solubility is of special value for topical application to open wounds or superficial dressings. It must be stated here that certain individuals show a considerable impairment of absorption and this must always be borne in mind when expected blood levels are not reached with standard doses.

Penicillin is readily soluble but unfortunately is rapidly destroyed in the acid medium of the gastric contents. This however is quantitative. If sufficiently large amounts are given significant blood levels may be reached. There would appear to be a number of factors which vary from individual to individual that make this method of administration open to chance. It will however be the ideal method when these problems are mastered.

Streptomycin is also readily soluble and can be given by mouth, but it is absorbed very slowly and a great amount so given can be recovered in the feces.

Acetylation — After absorption the sulfonamides are partially conjugated by the liver into acetylated forms which are therapeutically inactive and tend to be more toxic. This conjugation varies considerably with the different chemicals on the average in the following order: sulfapyridine 10 to 90 per cent, sulfathiazole 0 per cent, sulfanilamide 20 per cent, sulfadiazine 15 per cent, sulfaguanidine 5 per cent. This irregular and sometimes excessive conjugation has been an important factor against the use of sulfapyridine. This process does not occur with penicillin, streptomycin, etc., and therefore need not be discussed.

Distribution —Sulfonamides acquire an almost uniform distribution throughout the tissues and body fluids. There are however certain variations. Their concentration in tissues varies with the local vascular supply and is sometimes higher in exudates than in the blood. There are a few local variations. For instance sulfathiazole is present in relatively low concentration in the spinal fluid and the erythrocytes but it is in average concentration in the meningeal tissues and its absence in the red cells may account for the rarity of hemolytic anemia. Also in chronically infected areas where vascularization is deficient the concentration of sulfonamides may be relatively low.

The distribution of penicillin and streptomycin is not so uniform as with the sulfonamides. They will pass with difficulty if at all into the serous cavities and spinal fluid. Therefore in lesions of these areas they should be injected directly. It has been mentioned that the sulfonamides are almost inactive in purulent collections whereas penicillin is not retarded. Therefore its direct injection after aspiration of the purulent exudate is indicated.

Excretion – All sulfonamides except sulfaguanidine are excreted mostly by the kidneys. Small amounts are found in the secretions of milk, sweat, saliva and tears. The urinary excretion is by filtration and there is a moderate degree of reabsorption by the tubules. Increased diuresis by any means increases the output while renal lesions impair it. A single dose of 4 gm entirely disappears from the blood in twenty four hours except in the case of

However in the treatment of infections, time may be the essence of success Therefore the clinician may be on the horns of a dilemma He may be faced with several difficulties such as the imperative use of some possible specific agent immediately the impossibility of obtaining a specimen of material from the locus of the infection, lack of immediate facilities for the identification of the infecting agent even if such material can be obtained lack of facilities to determine whether the infecting agent even if identified is susceptible to chemotherapy or an antibiotic and finally the practicability of specific therapy

Although the ideal conditions for rational therapy are in the majority of cases lacking this may not always be the case It is impossible at the present time to place all patients who need such treatment in hospitals where the requisites mentioned above can be carried out In fact not all hospitals by any means could fulfill these requirements even if all such patients were so admitted This is no reason however that a rational procedure should not be carried out

It is now fairly well established that neither the sulfonamides penicillin nor streptomycin have an influence on the viruses known to be pathogenic to man with the possible exception of those of psittacosis and choriomeningitis which are yet unproved But there is increasing evidence that aureomycin is effective Therefore it would be unrealistic to use them for the common cold virus pneumonia vaccinia smallpox rabies encephalitis etc This does not exclude their use where there are secondary pyogenic infections as in smallpox where sulfadiazine and particularly penicillin are indicated and where from all indications streptomycin is the best of all The same can be said for the common cold and atypical pneumonia which although not proved virus diseases have not been benefited by their use but a secondary infection with the streptococcus staphylococcus Friedlander's bacillus or *H influenzae*, which may be the determining factor is vulnerable to one of these agents Chloromycetin is effective for gram negative infections

When we turn to the rickettsial diseases we find a similar situation There is no evidence that these agents have any influence on rickettsiae with the one exception that it has been established that penicillin inhibits the typhus rickettsia

On the other hand many bacteria and fungi are inhibited by sulfonamides penicillin, and streptomycin An outline will be given of the organisms and the diseases which are susceptible to these agents and to what relative degree they are considered susceptible (Tables XXII to XXIV) The same can be said of aureomycin There is increasing evidence that it has an effect on both viruses and rickettsiae (Table XXV)

Solubility and Absorption —Sulfanilamide is the only one of the sulfonamides which is readily soluble in water all the others are insoluble except as salts particularly the sodium combination However they become quite soluble in the body cells and fluids and also in the intestinal tract and are nearly completely absorbed in two to four hours when taken by mouth Sulfaguanidine is an exception It is very slowly absorbed and seldom in ordinary doses reaches a level of over 4 mg per cent in the blood It therefore has an

TABLE XXI

SYMPTOM	SULFANILAMIDE	SULFAPYRIDINE	SULFATHIAZOLE	SULFADIAZINE	SULFAGUANIDINE
Agranulocytosis	Rare	Rare	Less so	Less so	0
Anemia hemolytic	1.5%	1.0%	Very rare	Rare	0
Anemia secondary	5.0	2.0%	Rare	Rare	0
Anuria	0	0.5%	0.5%	Rare	0
Conjunctivitis	0	0	3.0%	0	0
Cyanosis	Common	Common	0	0	0
Dizziness	Common	Common	Rare	Rare	0
Episcleritis	0	0	0	Rare	1.0%
Fever	9.0	5.0	7.0	3.0	2.0%
Hematuria	0	10.0	8.0%	3.0%	0
Hepatitis	Rare	Rare	Rare	0	0
Neutropenia	1.0	2.0	2.0%	2.0	0
Acidosis	1.0%	4.0%	3.0	4.0%	0
Rashes	2.0	2.0%	4.0%	1.0%	2.0
Renal stone	0	0.5	0.5%	Rare	0.5%
Vomiting	30.0	60.0	0.0	5.0	0

great tendency to recur with any subsequent courses of treatment especially of the same drug but occasionally on exhibition of one of the others. It is best to cease all sulfonamide therapy unless the risk is less than the benefit expected from their continuance in controlling an originally severe infection for which these drugs are known as a specific.

c *Renal Stones*.—The deposits in the renal system are due to the acetyl fractions. Hematuria may be either microscopic or macroscopic. The most minor manifestation is a crystalluria. This may be a passing phase. On the other hand it may increase to extensive deposits in the renal tubules, large *concretions in the pelvis and finally complete blockage of the ureters* leading to hydronephrosis and anuria. This may occur with all sulfonamides except sulfanilamide and sulfaguanidine and of course calls for immediate stoppage of the drug. It is best combated by rendering the urine alkaline and promoting polyuria by the copious ingestion of fluids. At least 1,200 c c should be taken each day. Surgical interference may be required.

d *Hematological Changes*.—Hemolytic anemia of severe degree may develop with explosive suddenness. It is important therefore to keep a vigilant watch for its occurrence. This may occur during the early days of therapy and on occasion is wrongfully attributed to the infection. As agranulocytosis develops later in the course (after 12 days) *it is well to check the white count every few days*.

The toxic effects of the antibiotics are comparatively minor compared to those of the sulfonamides. Penicillin may cause skin rashes and occasionally a serum sickness like reaction. Since various salts of penicillin have been introduced such as Na, Li, NH, Sr, Ca, Mg and K the *toxicity in experimental animals has been increased*. It was concluded therefore that the toxicity of penicillin salts is primarily due to the cations used in their preparation.

Streptomycin exhibits very few toxic effects in man. There is sometimes a histamine like reaction characterized by nausea, headache, *general malaise*, skin rashes, arthralgia, vasodilation and fever. The second complication which is a serious one is the occurrence of a vestibular dysfunction and deaf

sulfadiazine which is slower While both the free and acetylated forms are freely excreted by the kidneys, the latter may give rise to trouble through precipitation in the tubules pelvis, and ureters to form casts in the first, stones in the second and sedimental blockage in the third These conditions are enhanced by acid urine and oliguria and reduced by alkaline urine and polyuria Therefore adequate intake of fluids is advantageous and excessive amounts may reduce this danger to a minimum but by excessive diuresis prevent adequate concentration in the blood and tissues

Both penicillin and streptomycin are readily and harmlessly excreted through the kidneys This is one of the principal difficulties in the maintenance of high blood levels even by repeated parenteral injections There would appear to be considerable evidence to indicate that penicillin is excreted by the tubules Therefore attempts have been made to reduce or block this by giving substances which are also excreted by this means The first to be used was hippuric acid but this had serious gastrointestinal side effects More recently other substances have been used with encouraging results This is important as in cases where high blood concentration are required on account of the relative resistance of the organism satisfactory results can only be so obtained by such means or else by increasing enormously the amount of antibiotic given Like procedures may be necessary for streptomycin

It has been stated above that streptomycin is not readily absorbed by the bowel The contrary may also be said of its excretion into the bowel In other words, the intestinal wall is almost impervious to its passage

Toxic Effects—*One of the drawbacks of chemotherapy is the toxic reactions although these on the whole are not really of much consequence if kept in mind* These toxic results may be primary so to speak in persons who have not previously taken the drug On the other hand similar effects more often develop as an evidence of sensitization through previous administration Although the latter occurs in about 2 to 5 per cent of cases it may not seem important until it be appreciated that these drugs are unfortunately taken and/or given promiscuously for all and sundry conditions whether indicated or not It is most important that this should be appreciated as there is being built up a large number of people who may be sensitive and when a really serious illness occurs the drug may not be given with safety *In fact, one of the crimes of modern therapeusis is the promiscuous use of new drugs without reason or understanding* The principal toxic symptoms and their relative frequency are found in Table XXI

It is true that the majority of these symptoms and signs are of little importance but there are four which should be taken seriously

a *Fever*—This is of most importance as it may lead to a misunderstanding as to course of the disease *The fever of the infection* except in complicated or unsuitable cases is usually normal in about 3 to 4 days Therefore if there has been clinical improvement and the pyrexia continues it must be suspected as being due to the drug and its use should be discontinued If this be the case the temperature will return to normal within 48 hours

b *Skin rashes* are chiefly of importance as they may be a precursor of an exfoliative dermatitis Rashes usually occur early in the therapy and have a

The dosages to attain these levels when administered by mouth, but with due allowance being given to individual variations in the rate of intestinal absorption are as follows

Sulfanilamide—initial dose 3 to 5 gm followed by 1 gm every 4 hours day and night
Sulfapyridine—initial dose 3 to 4 gm followed by 1 gm every 4 hours day and night
Sulfathiazole—same as sulfapyridine
Sulfadiazine—initial dose 3 to 4 gm followed by 1 gm every 6 hours day and night
Sulfamerazine—initial dose 3 to 4 gm followed by 1 gm every 8 hours day and night
Sulfaguanidine—initial dose 5 to 10 gm followed by 3 to 5 gm every 4 hours day and night
Sulfasuxidine—10 to 15 gm followed by 3 gm every 4 hours day and night

It must be remembered that *sulfadiazine* and *sulfamerazine* are slowly excreted by the kidneys and that sulfaguanidine is slowly absorbed, in fact, the majority of the latter remains in the bowel contents and hence has an almost local action on intestinal flora and with diarrhea a great part is found in the stools

Intravenous and subcutaneous therapy is usually confined to the initial dose unless it is impossible to give by mouth and for this the same amounts are employed in the form of the sodium salts but are repeated at longer intervals—6 to 8 hours for the first three days and 12 hours for sulfadiazine and sulfamerazine Sulfaguanidine and sulfasuxidine are never given parenterally

Penicillin is usually given intramuscularly If in plain solution the intervals are every three hours day and night This adds a considerable burden to the physician or nurse and is often objectionable to the patient The intravenous routine is more exacting and distressing if the therapy has to be maintained over a prolonged period of time Furthermore as the blood level must be maintained fairly constant throughout the twenty four hours sleep is continually being disturbed To avoid these objections and other minor ones the principle of administering it by intramuscular injection in a beeswax and peanut oil mixture as in histamine and desoxycorticosterone acetate therapy was explored This was found to be successful in that the slow absorption permitted fairly constant blood levels (0 1 to 0 5 units per c c) to be maintained for six to eight hours What might be termed adequate levels were attained when 40 000 to 60 000 O U were injected in 2 5 c c of this mixture Such injections may be given three times a day or three hourly injections in aqueous solution may be given during the day and a beeswax and oil injection given at bedtime to insure a continuous period of sleep Further advantage is to be found in conditions where short periods of penicillin action (12 hours) are sufficient as for example in acute gonorrhea 200 000 units in 2 c c of beeswax oil mixture will usually be successful It is now usually agreed that the procaine salt of penicillin suspended in sesame oil containing 300 000 units of penicillin per c c is easily administered tolerated without discomfort has few toxic features and maintains fair plasma levels of the drug from sixteen

ness The former is by far the more frequent Whereas at first there was usually a residuum, with the reduction in dosage the frequency of vestibular impairment has been conspicuously less

An increasing number of cases are being reported of what might be considered an avitaminosis when penicillin, streptomycin sulfaguanidine, or even sulfadiazine have been given by mouth The symptoms and signs are usually described as resembling those of nicotinamide or riboflavin deficiency and some have a more extensive suggestion of a pellagrous condition In some an estimate of the daily urinary output of nicotinamide and riboflavin has shown them to be markedly deficient All symptoms promptly disappeared on cessation of the drug and institution of vitamin therapy preferably by the parental route The exact cause of these secondary reactions is not yet clear but it is suggested that they are due to a pronounced decrease in the intestinal flora The stools can be rendered sterile by streptomycin and on occasion by sulfaguanidine It could be surmised that in the cases associated with penicillin and sulfadiazine they were of those unusual groups in which these substances pass through the stomach unaltered as in penicillin and that in both the absorption is impaired Further work is necessary, but these cases sound a note of warning

The toxic effects of aureomycin are very few and up to the present consist of a variable degree of nausea and vomiting Reduction in the dosage or temporary withdrawal of the drug is usually effective The use of 0 5 ounce of aluminum hydroxide with each 100 mg oral dose has been advocated

Method of Administration and Dosage.—Oral administration is the method of choice for all the sulfonamides unless there is an immediate demand for a high blood level If this be required sulfanilamide being highly soluble in water may be given subcutaneously in an 0 8 per cent solution in physiological saline The other sulfonamides are best given intravenously as the sodium salts of a 5 per cent solution in distilled water Topical applications are also used but on account of its solubility sulfanilamide gives by far the best results by this means

The dosage depends upon the following several factors which it is well always to keep in mind the type of organism the acuteness of the process the severity of the primary systemic reaction the rate of absorption renal function and the state of hydration Under such conditions each case must be considered individually as the habit of routine procedure is sure to lead to trouble and in fact is a frank acknowledgment of unreasoned practice When possible the course of the therapy should be followed by daily estimation of the blood levels of which there is an optimum for each drug (free)

	MG PER CENT
Sulfanilamide	10 to 1
Sulfapyridine	5 to 10
Sulfathiazole	5 to 10
Sulfadiazine	5 to 10
Sulfamerazine	5 to 10
Sulfaguanidine	1 to 3
Sulfasuxidine	1 to 3

The dosages to attain these levels when administered by mouth, but with due allowance being given to individual variations in the rate of intestinal absorption are as follows

- Sulfanilamide—initial dose 3 to 5 gm followed by 1 gm every 4 hours day and night
- Sulfapyridine—initial dose 3 to 4 gm followed by 1 gm every 4 hours day and night
- Sulfathiazole—same as sulfapyridine
- Sulfadiazine—initial dose 3 to 4 gm followed by 1 gm every 6 hours day and night
- Sulfamerazine—initial dose 3 to 4 gm followed by 1 gm every 8 hours day and night
- Sulfaguanidine—initial dose 5 to 10 gm followed by 3 to 5 gm every 4 hours day and night
- Sulfasuxidine—10 to 15 gm followed by 3 gm every 4 hours day and night

It must be remembered that sulfadiazine and sulfamerazine are slowly excreted by the kidneys and that sulfaguanidine is slowly absorbed in fact the majority of the latter remains in the bowel contents and hence has an almost local action on intestinal flora and with diarrhea a great part is found in the stools

Intravenous and subcutaneous therapy is usually confined to the initial dose unless it is impossible to give by mouth and for this the same amounts are employed in the form of the sodium salts but are repeated at longer intervals—6 to 8 hours for the first three days and 12 hours for sulfadiazine and sulfamerazine Sulfaguanidine and sulfasuxidine are never given parenterally

Penicillin is usually given intramuscularly If in plain solution the intervals are every three hours day and night This adds a considerable burden to the physician or nurse and is often objectionable to the patient The intravenous routine is more exacting and distressing if the therapy has to be maintained over a prolonged period of time Furthermore as the blood level must be maintained fairly constant throughout the twenty four hours sleep is continually being disturbed To avoid these objections and other minor ones the principle of administering it by intramuscular injection in a beeswax and peanut oil mixture as in histamine and desoxycorticosterone acetate therapy was explored This was found to be successful in that the slow absorption permitted fairly constant blood levels (0 1 to 0 5 units per c c) to be maintained for six to eight hours What might be termed adequate levels were attained when 40 000 to 60 000 O U were injected in 2 5 c c of this mixture Such injections may be given three times a day or three hourly injections in aqueous solution may be given during the day and a beeswax and oil injection given at bedtime to insure a continuous period of sleep Further advantage is to be found in conditions where short periods of penicillin action (12 hours) are sufficient as for example in acute gonorrhea 200 000 units in 2 c c of beeswax oil mixture will usually be successful It is now usually agreed that the procaine salt of penicillin suspended in sesame oil containing 300 000 units of penicillin per c c is easily administered tolerated without discomfort has few toxic features and maintains fair plasma levels of the drug from sixteen

to sixty hours after injection It would seem probable that this manner of administration will prove quite satisfactory for most infections when indicated The consequent economy of nursing effort will be most welcome

Penicillin given by mouth in tablets to be sucked are sometimes useful for local buccal and pharyngeal infections but many doubts are raised in this regard The period when a concentration of any degree is maintained is fleeting and the influence is superficial On the other hand, with improved pharmaceutical preparations the oral route for attaining adequate blood levels with certainty may be accomplished Until this be the case the chances of error are too great for this method to be advocated for general purposes

Inhalation or "aerosol" therapy for penicillin has given excellent results in selected cases of laryngeal and bronchial infections due to susceptible organisms The penicillin is nebulized by a variety of means and inhaled at regular intervals

It has been mentioned above that penicillin does not pass as readily as would be hoped through inflamed serous membranes or the meninges Therefore intrapleural intrapericardial intraperitoneal and intrathecal administration of a solution of the sodium salt is often an important accessory to its parenteral use This is important as contrary to sulfonamides penicillin is active in purulent exudates

The dosage of penicillin varies considerably in different infections This variation is interpreted in two ways first the daily amounts and second, the number of days it is to be continued In general the daily dose amounts to from 100 000 to 480 000 units This may be given in equally divided doses every three hours in two doses in beeswax and oil or as one dose, by the procaine salt in sesame intramuscularly once a day or by continuous intravenous or intramuscular drip As far as the action of the penicillin is concerned the method is immaterial provided an adequate and fairly continuous blood level is maintained

The duration of the therapy represents much greater variations which may range from a single dose in beeswax and oil or the procaine salt to the continuous therapy over weeks in subacute bacterial endocarditis It may be laid down as a general rule that in acute infections treatment from a few days to a week is sufficient while in the subacute and more chronic cases this may extend to thirty or more days

Streptomycin may be given after the same methods as used for penicillin There are however several variations In the first instance it can be readily and effectively given by mouth by which method a satisfactory blood level can be maintained Furthermore the contents of the gastrointestinal tract are converted temporarily to a sterile state but a few days after its withdrawal the growth of organisms returns On the other hand it has the drawback that when given by the intrathecal route it produces what appears to be a foreign body reaction Bacteria as a rule appear to become resistant to streptocomycin more readily than they do to penicillin Therefore the initial dosage should be relatively large if the course is to be of short duration

The dosage of streptomycin varies somewhat according to the method of administration It must first be stated that it may be prescribed either as

units or by weight—1 000 units being equivalent to 1 mg of pure streptomycin or 1 000 000 units equal to 1 gm. Experience is not yet sufficient to be at all dogmatic as to the exact amounts which are indicated in any specific infection. As with penicillin the sensitivity of the organism is an important determining factor as is also its virulence to man. The level in the blood should be about 30 mg per c c at the peak. The average amounts by different methods of administration are usually as follows

Intravenous administration	1 to 2 gm daily in 6 doses
Intramuscular administration	1 to 2 gm daily in 6 doses
Oral administration	0.5 to [illegible] gm daily in 4 doses
Aerosol administration	0.5 gm daily
Intrathecal administration	0.5 gm daily

Although streptomycin is rapidly excreted in the urine the blood level falls more slowly than does penicillin. Therefore the intervals between administrations may be longer. It has been stated that streptomycin is poorly absorbed by the intestinal tract. The same is true for the aerosol method. But by parenteral injections a high blood level may be maintained since it can be recovered from ascitic and pleural fluids, aqueous and vitreous humours, amniotic fluid and bile. Only traces can be found in the normal spinal fluid but in acute inflammation of the meninges levels as high as 25 mg per c c are reported. It is well therefore to determine this level if possible before intrathecal administration is used.

Aureomycin is usually given by mouth as on account of its high acidity there are difficulties for the parenteral routes. It can however be given intravenously by syringe in a 5 per cent solution in 20 c c of distilled or in 500 c c in a proportionately weaker dilution. A procaine solution has been used intramuscularly but is not advised with present preparations. The dosage of aureomycin by the oral route is 5 to 10 mg per kilogram of body weight every 6 hours or 0.5 to 1 gm for an ordinary adult.

Indications for Therapy.—It may be simply stated as a law that chemotherapeutic or antibiotic agents are indicated when a pathogenic infection is due to an organism which is sensitive to any one or more of them. Their indiscriminate use without knowledge of the probable organism and their possible value before making every effort to obtain a culture of material as a source of this information is the worst form of "shotgun" therapy. It is true that apparently good results may occur but one of the greatest hazards in rational therapeusis is what appears to be coincidence which really rests upon the fact that most infections are self limited and specific therapy is often given at the height of the disease. This is one of the principal fallacies of the "catch as catch can" conclusions of clinical therapeutics where the failures are forgotten or not given their proper weight. On the other hand critical and analytical clinical observations have been the basis for therapeutic advances whether it were digitalis in congestive circulatory failure, quinine for malaria, mercury for syphilis, cowpox vaccination against smallpox, thyroid extract for myxedema or cretinism, cod liver oil or sunlight against rickets, or citrus fruits for scurvy. In their use the deduction of cause and

effect was fairly simple and direct, but in most infections there are several variables which must always be taken into consideration. These are:

1. What is the infecting organism specific for the disease syndrome such as tularemia, typhoid fever, tuberculosis, rabies, syphilis, Rocky Mountain spotted fever, etc.?

2. What is the organism responsible for a nonspecific infection such as pneumonia, bacterial endocarditis, meningitis, sinusitis, peritonitis, enterocolitis, pleurisy, etc.?

3. Is the specific causative agent of the disease or nonspecific organism sensitive to chemotherapy or antibiotics?

4. How virulent is the causative agent to the human organism? It is well known that *Staphylococcus aureus* in systemic infections is much more virulent than when localized in a furuncle or carbuncle and a much greater hazard on the average than is the *Streptococcus hemolyticus* in all forms. Also the gonococcus is as a rule a more benign pathologic agent than is the meningococcus. Other examples might be given, but these would seem sufficient.

5. Where is the infection located? Is it local or systemic? Is it best attacked by local, oral, intrapleural, intravenous, intramuscular or intrathecal methods of administration?

TABLE XXII

SUSCEPTIBILITY OF LIVING ORGANISMS TO SULFADIAZINE AND SULFAGUANIDINE

HIGHLY SUSCEPTIBLE ORGANISMS	
Sulfadiazine	Sulfaguanidine
N. meningitidis	*S. dysenteriae*
Str. hemolyticus	
N. gonorrhoeae	
D. pneumoniae	
MODERATELY SUSCEPTIBLE ORGANISMS TO SULFADIAZINE	
K. pneumoniae	
B. anthracis	
Cl. welchii	
Cl. septicum	
H. influenzae	
Staph. aureus	

TABLE XXIII

SUSCEPTIBILITY OF THE LIVING AGENTS OF DISEASE TO PENICILLIN

HIGHLY SUSCEPTIBLE ORGANISMS		
B. anthracis	*Cl. tetani*	*Staph. albus* (most strains)
B. subtilis	*Cl. tetanomorphum*	*Staph. aureus* (most strains)
Cl. histolyticum	*C. diphtheriae*	*Str. bovis*
Cl. novyi	Diphtheroid bacilli (most strains)	*Str. equinus*
Cl. oedematiens	*D. pneumoniae*	*Str. pyogenes*
Cl. welchii	*H. ducreyi*	*Str. hemolyticus* (except group D)
Cl. septicum	*N. catarrhalis*	*T. pallidum*
Cl. sporogenes	*N. gonorrhoeae*	*R. prowazeki* (murine typhus)
Cl. sordellii	*N. intracellularis*	
MODERATELY SUSCEPTIBLE ORGANISMS		
A. bovis	*Cl. chauvoei*	*S. minus*
Anaerobic streptococci	*Ery. rhusiopathiae*	*Str. faecalis*
Bor. novyi	*Lept. icterohaemorrhagiae*	*Str. lactis*
Bor. recurrentis	*M. lysodeikticus*	*Str. nonhemolyticus*
Cl. bifermentans	Ornithosis virus	*Str. salivarius*
Cl. botulinum	Psittacosis virus	*Str. viridans*

6 Should a short intensive course be given or will it require a prolonged course and how concentrated should blood levels be?

All of these questions must be analyzed and answered by the physician to himself. But there are certain criteria which may help him to arrive at a conclusion. These rest upon the relative susceptibility of the various organisms to the different sulfonamides and penicillin, streptomycin or aureomycin. These are listed in Tables XXII to XXV.

TABLE XXIV

SUSCEPTIBILITY OF THE LIVING AGENTS OF DISEASE TO STREPTOMYCIN

HIGHLY SUSCEPTIBLE ORGANISMS	
A. aerogenes	*H. influenzae*
Br. abortus	*H. pertussis*
Br. suis	*M. mallei*
D. pneumoniae	*N. gonorrhoeae*
E. typhi	*S. schottmulleri*
Ery. murisepticae	*Str. hemolyticus*
MODERATELY SUSCEPTIBLE ORGANISMS	
B. anthracis	*Myco. tuberculosis hominis*
B. mycoides	*Past. pestis*
B. subtilis	*Past. tularensis*
C. diphtheriae	*S. paradysenteriae*
Esch. coli	*Staph. aureus*
K. pneumoniae	

TABLE XXV

SUSCEPTIBILITY OF LIVING ORGANISMS TO AUREOMYCIN

E. typhosa	*D. pneumoniae*	*Staph. aureus*
Esch. coli	*N. gonorrhoeae*	
K. pneumoniae	*N. meningitidis*	
A. aerogenes	*Br. melitensis*	
H. influenzae	*Br. abortus*	
Str. pyogenes	*Br. suis*	

As yet the susceptibility of many organisms to aureomycin has not been determined accurately. However, it is the first antibiotic applicable to man which reveals evidence of being effective against rickettsiae and viruses. A tentative list includes those believed to be the causative agent in the following diseases: lymphogranuloma venereum, granuloma inguinale, psittacosis, virus pneumonia, trachoma, murine epidemic and scrub typhus, Rocky Mountain spotted fever, South African tick bite fever, rickettsialpox, North Queensland tick fever and seven strains of Q fever.

It will be seen from the above that certain pathogenic agents are susceptible to one or more of the sulfonamides and antibiotics, but this is relative. There has been a constant endeavor to arrive at a quantitative assessment of their relative values and this has been solved after a rather empirical fashion. By this is meant that the variables in human disease cannot be always compared with a controlled experiment. In spite of this much has been accomplished in the prevention and cure of disease.

Prophylaxis.—It has now been accepted on somewhat disputed grounds that certain diseases can be mitigated or recurrences even prevented by the use of some of these agents. The following may be considered.

Rheumatic Fever.—The supposed increase of recrudescences of rheumatic fever parallel with the mounting prevalence of *Streptococcus hemolyticus* flora in the nasopharynx has led to the custom of giving sulfadiazine in minimal doses over a prolonged period (years) with the object of reducing this flora during vulnerable periods (see Rheumatic Fever, page 67). The validity

of this procedure may be doubted, but the fact remains that we are so helpless in the face of this disease that any straw is worth grasping. The only hazard is in the probability that the streptococcus if present will become resistant to one or another of these agents. This may be unavoidable, but is not so serious as the possibility that the host may become sensitive to the drug.

Streptococcus Sore Throat.—A somewhat similar result has been obtained in the handling of this condition in groups of recruits in schools, etc., where young people or children live in close contact. The use of 0.5 gm. of sulfadiazine twice a day has produced a conspicuous reduction of cases. This is primarily applicable to air borne infections and not to milk, which is best handled by detection of a carrier among the milk handlers or in the kitchen and pasteurization of the milk.

Scarlet Fever.—The same method may be employed for contacts with scarlet fever, but it should not be advocated for the population in general both on account of the risk of toxic reactions and the production of sulfonamide resistant strains.

Gonorrhea.—It has now become an accepted custom for prostitutes and their habitual consorts to take sulfonamides (sulfadiazine) or penicillin by mouth as a protective against gonorrhea. Their value to the consorts is dubious; as for the prostitutes it is even more so as it has been demonstrated that in time they may and often do harbor a resistant strain of this organism which although attenuated to them is virulent to another host.

Parturition.—There are on occasion reasons to believe that a gonorrheal infection may be reactivated or the probability of a primary pyogenic infection initiated which might lead to a septicemia or even a bacteriemia. It is therefore proper to give either sulfadiazine or penicillin in proper amounts to forestall such an infection. The pyogenic organism is usually the streptococcus. If another bacterium is subsequently isolated as the causative factor, the most efficient drug should be employed.

Smallpox.—The use of sulfonamides and the antibiotics to control the staphylococcal infection of the skin lesions of this disease and varicella has given most encouraging results. They should be started as soon as the vesicles appear and be continued until the crusts have fully desiccated and are spontaneously dropping off.

Preoperative.—It has become a custom with many surgeons to give a short course of penicillin before *all* operations and to continue for several days afterwards. The rationale is to prevent secondary infections. This would hardly seem necessary unless there were a fear of a break in the aseptic technic. Such procedures often give a sense of false security and such breaks are then more likely to happen.

On the other hand, there are some operations which require through their very nature that healthy tissues may be soiled by infected material or that there is a great hazard that this might occur. Therefore the agent which is effective against the organism which is most likely to be the principal pathogen should be used after a prophylactic manner.

Operations upon the large bowel and rectum are notoriously hazardous as to secondary infections. The sulfonamides and penicillin were indifferently

useful in combating these conditions but streptomycin has been conspicuously successful It should be given by mouth (1 to 2 gm per day) for 3 to 4 days before the operation This will practically suppress bacterial growth in the feces Immediately following the operation it may be given intravenously or intramuscularly in the same amounts for a few days It has been pointed out above that there is little or no transfer of streptomycin through the bowel in either direction therefore it should be given in a proper sequence

Leucopenia—In a number of acute infections a leucopenia is characteristic In most of these secondary infections with pyogenic organisms are fairly common particularly as furuncles carbuncles impetigo or pneumonia The following is a list of these diseases typhoid fever typhus influenza Rocky Mountain spotted fever measles malaria virus pneumonia, etc It is therefore proper to use the proper drug against the pyogenic agent which is chiefly the *Staphylococcus aureus* in spite of the fact that it is of no value in the original disease

There are conditions which are not primarily infections in which these drugs are of great value such as in agranulocytic angina and in the aleucemic phase of leucemia The organisms which are most commonly accountable for the angina in these diseases are the staphylococcus and the streptococcus Therefore penicillin in full doses (400 000 to 500 000 units per day) should be given with complete appreciation that it is used for prophylaxis of infection and not for cure of the original condition

The prophylactic use of these agents under specific conditions does not imply that they should be used as a routine for the prevention of for instance pneumonia erysipelas scarlet fever meningococcus meningitis etc Such a program would undoubtedly do great harm but unfortunately it is done by the laity far too often

Curative Therapy—In addition to the prophylactic use of these agents there will now be considered their curative value and range of use It should be a fundamental rule that the agent of choice should be so administered as to reach the locus of infection in the greatest concentration This is usually attained through *the blood stream by intravenous or intramuscular injections* but there are circumstances which would indicate that additional methods should also be used These may be summarized as follows

1 In pharyngeal laryngeal bronchial and pulmonary lesions the parenteral method should be supplemented by the aerosol method for penicillin In fact the latter may be used exclusively in chronic lesions

2 In enterocolonic lesions streptomycin when indicated for a specific organism should be given both by mouth and parenterally The latter method is always indicated during the acute stages and the former in the more chronic conditions but both methods have their place under particular circumstances Vigilance should always be exercised to detect the remote but real secondary results as mentioned above (see page 1431) Aureomycin and streptomycin have also given encouraging results when used in typhoid fever and gram negative bacillary lesions in the urinary tract They also would appear to be effective in undulant fever

3 When the serous cavities, the joints, the paranasal sinuses, the middle ear, and the meningeal space are involved, direct injection of penicillin or streptomycin where indicated should be employed.

4 The topical application of sulfanilamide, penicillin, and more rarely streptomycin or aureomycin may be used in cutaneous lesions and other accessible local lesions. But these conditions usually, but not always, require also parenteral therapy.

Although through the previous text many statements have been made as to when these agents are indicated, it is now considered proper to summarize these for easy reference (see Table XXVI). It must be appreciated, however, that this summary is not absolute, as with experience their relative value and further extension or contrariwise leaves this question in a constant state of flux.

TABLE XXVI

Pneumococcus
- Penicillin—320 000 O U per day intramuscularly and continued until temperature is normal for five days
- Sulfadiazine—6 gm per day by mouth until the temperature is normal for five days. An initial dose of 4 gm should be given intravenously in severe cases

Friedlander Bacillus
- Streptomycin—2 gm per day intramuscularly until the temperature is normal for five days
- Sulfadiazine—as given for pneumococcus infections

Staphylococcus
- The agents of choice are the same as for the pneumococcus and after the same dosage and method

Streptococcus
- The agents of choice are the same as for the pneumococcus

Meningococcus
- Sulfadiazine—6 gm per day by mouth until the temperature is normal for one week and the spinal fluid is sterile
- Penicillin—15 000 O U intrathecally and 240 000 O U intramuscularly until the temperature is normal for one day

Gonococcus
- The agents of choice are the same as for the meningococcus and should be used in the same amounts in severe cases but shorter period as usually sufficient in early local infections

H Influenzae
- Sulfadiazine—6 gm per day until the temperature is normal for five days
- Streptomycin—1 gm per day intramuscularly until the temperature is normal for five days. Streptomycin is only indicated in severe pneumonia, meningitis, endocarditis, bacteriemia, etc due to this organism

It will be noted from Table XXV that aureomycin may be substituted on occasion for either sulfonamides or penicillin or streptomycin. But it would appear that it has a unique influence upon rickettsial and viral infections. In addition to those already mentioned it has been found to be efficacious in the viral infections of the eye.

These are examples of the dosage and methods of therapy against a few of the common organisms which are sensitive to these agents. It must be appreciated that all infections are not of the same virulence and may affect different tissues. A good example is in the case of the *Streptococcus viridans*. This is usually an organism of mild pathogenicity but when it is the cause of subacute bacterial endocarditis, although the course was long and often com

paratively mild the end result was usually fatal But penicillin used in full doses as above and continued for at least 28 days irrespective of the absence of symptoms usually brings about a complete cure It must be ascertained however, that the strain of the organism is sensitive and does not become resistant and that a sufficiently adequate blood level is maintained

At the present time the value of streptomycin in the treatment of tuberculosis is in the stage of investigation There is no doubt that it is an effective agent against the *Myco tuberculosis* in experimental animals but it is difficult to translate these into practice in man where the variety of the anatomical changes are so diverse It would seem logical that it would be most efficacious in the early exudative stages whether in children or adults It would be immaterial whether such a lesion were in the pharynx larynx bronchus long parenchyma etc Miliary tuberculosis would seem to offer a good hope of a satisfactory result When tuberculous meningitis is present however the results have not been as satisfactory as could be wished There is little doubt that life is prolonged but the final result seems to be partly influenced by a foreign body reaction in the meninges which so often occurs There is one important fact that must always be borne in mind This is the ease with which the *Myco tuberculosis* acquires a resistance to the antibiotic There appears to be a growing tendency to employ streptomycin in all and sundry types of tuberculous infection This is to be condemned It may be stated according to our present knowledge that it should not be used under the following conditions (1) Early minimal parenchymal lesions which would be expected to respond favorably to a rest cure with or without collapse therapy (2) Advanced fibro ulcerative lesions (except in the below) (3) It should not be used in ambulant cases to the exclusion of a rest cure and/or collapse therapy On the other hand its use is indicated in the following (1) Miliary tuberculosis (2) An exudative parenchymal lesion which is not responding favorably to rest cure with or without indicated collapse either on account of local spread or continuing severe systemic reaction (3) Acute tuberculous pneumonic lesions (4) Tuberculous lesions which militate against a proper cure such as tuberculous pharyngitis laryngitis or tracheitis if the first is a serious hazard for nutrition and the last two through severe coughing paroxysms rob the patient of rest (5) Tuberculous bronchitis without evidence of fibrotic stenosis or a distal parenchymal lesion for which future surgical interference would be indicated (6) In preparation for major surgical operations such as thoracoplasty and particularly lobectomy or pneumectomy and also following such operations to prevent possible local or contralateral spread

It must be emphasized that the use of streptomycin is at present in an exploratory stage Future experience may and probably will modify our present concepts but for the present it must be appreciated that there is much still to be learned from critical and well controlled observations

Aureomycin is one of the more recent antibiotics which has become available for use in human disease It holds great promise as a valuable agent against certain rickettsiae and viruses as outlined in the footnote to Table XXV The exact manner of its action in these infections is not at present

known, but it is hoped that in the near future this will be clarified as this may unmask an entirely new field of intracellular pharmacology It would seem that it acts as a bacteriostatic agent to the organisms in bacterial diseases, many of which are also vulnerable to the sulfonamides penicillin and streptomycin, and also it is antagonistic to certain gram negative organisms which have so far been resistant to the agents But this may not necessarily be so in the case of the rickettsiae and viruses

The impetus given to the exploration for new antibiotics is opening up a constantly broadening field in human therapeutics Many antibiotics have been discovered but relatively few are applicable to man There are some, such as chloromycetin which hold great promise but it is hoped that the use of all will be properly evaluated before our enthusiasm runs away with knowledge and common sense

CHAPTER XXI

DISEASES DUE TO ALLERGY

INTRODUCTION

The role of allergy in the causation of anatomical and physiological dis turbances in the body has come into prominence during the last generation The rapid advances made in this conception of the etiology of disease have led *to considerable confusion in the definition or interpretation of a number of* terms which it would be well to clarify before we proceed further

Immunity is that state of individual cells or the organism as a whole which protects them from the deleterious action of bacteria or foreign pro teins or other chemicals

Anaphylaxis was applied in 1893 by Richet to indicate a state in which there was increased susceptibility increased sensitiveness or hypersuscepti bility to similar substances in contrast to immunity

Allergy should be defined as that state where there is an altered reaction which may be either more rapid or more intense to these substances In many instances it is synonymous with the older more general and less definite term of *idiosyncrasy* It is now usually accepted that *allergy* is inclusive of or synony mous with hypersensitiveness sensitization idiosyncrasy anaphylaxis and atopy As far as is known decreased susceptibility or immunity to bac teria, foreign proteins or other chemicals does not produce any disease pattern There is little doubt that confusion still exists in the interpretation of clinical anaphylaxis and/or allergy Before proceeding further it would be well to deal with what is commonly known as serum disease or serum sickness

SERUM DISEASE OR SERUM SICKNESS

Serum sickness is used to describe a series of phenomena which sooner or later develop in individuals who are sensitive to the serum employed The response may be either immediate or delayed It would probably be better if the usage of these terms were restricted to the delayed or late phenomena which sometimes go by the term normal serum disease The symptoms are supposed to be produced by the foreign protein in the serum and not by any specific antitoxic opsonic lytic or agglutinating properties which the serum may have Therefore there has been a continuous attempt made to render all protective sera as free of proteins as possible and as this cannot be completely accomplished the protective bodies are concentrated in a solu tion which contains small protein fractions and can be administered in small amounts The majority of protective sera are manufactured by immunizing horses Therefore the most common forms of serum sickness result from the injection of horse serum and this will be taken as the example to illustrate this condition

Incidence—There are considerable differences in individual susceptibility to horse serum and about 10 per cent of people can tolerate large amounts This is probably due to their being very slightly susceptible rather than completely immune North American Indians and Negroes are less susceptible than the white race There is every reason to expect that a person who has had serum more than fourteen days previously will be more or less susceptible, but there are many who have never had such injections but may be equally so Therefore it is always wise, before serum is given, to determine the susceptibility of the individual This can be done either by skin reactions or by the intravenous injection of minute quantities

Symptoms—The incubation period is modified by whether or not the patient has had serum previously If it be the first injection, symptoms usually appear in from six to twelve days and rarely after two to three weeks If he has had serum previously, this period may be considerably shortened The first sign, if sought for is a general adenopathy and occasionally a palpable spleen These may precede the appearance of skin rashes by several days The latter, however, are the first symptoms of which the patient complains The eruption usually begins as an urticaria in irregular wheals This is soon followed by localized or diffuse erythema and there is considerable pruritus The rash is sometimes morbilliform or scarlatiniform and rarely purpuric The distribution may be either patchy or diffuse Pyrexia occurs in about 30 per cent of the cases as does also edema The former may range from 100° to 104° F The latter may vary considerably and is most prominent in the face, particularly about the eyes Its general distribution is irregular not only in degree but also in extent and may even simulate the edema of nephritis With it there is a definite chloride and water retention with albuminuria and casts In rare instances nitrogen retention has been reported Another common occurrence is arthritis The incidence of this varies from 20 to 60 per cent of the reported series of cases There are usually pain, tenderness and limitation of movement of one or more joints In a small number of these cases there are also swelling redness tenderness and signs of exudate which is of an inflammatory nature containing many cells, up to 25 000 or 30 000 per cubic millimeter, principally granulocytes although mononuclear cells are also present The arthritis develops several days after the eruption Occasionally edema and hyperemia of the retina and optic discs have been reported as have also optic neuritis and signs of spinal fluid involvement as indicated by increased number of cells and globulin in the spinal fluid

Other signs and symptoms of less conspicuous frequency are vomiting, diarrhea abdominal cramps and headache which is often intense when associated with changes in the spinal fluid and there may also be profound lethargy The changes in the leucocytes vary with time There may be a definite eosinophilia and an immediate leucopenia especially in children followed by a leucocytosis or the leucocytes may return to normal In the European literature there have been a number of cases reported of polyneuritis developing later in the course of the illness Recurrences of the rashes are sometimes observed, and these are most apt to be morbilliform

Pathological Anatomy—There has not been much opportunity to investigate the anatomical changes in man The cause of these symptoms is attributed to the presence of precipitins or other antibodies They may be present in the cells or free in the plasma and by about the seventh to the ninth day, or thereafter, are present in sufficient concentration to give a reaction with the antigen if it be injected The violence of this reaction depends upon three factors concentration of the antibodies the amounts of the antigen injected, and the route of the injections the four of which give intensities of reaction in the following ascending order—intradermal, subcutaneous intramuscular and intravenous *It will be seen, therefore, that the concentration of the antigen in the plasma at any one instant plays an important role in the violence of the reaction* The exact manner whereby these symptoms are produced has been the subject of much discussion and experiment There is not necessarily any direct relationship between the amounts of antibody in the plasma and the severity of the systemic reaction It would appear more probable that the higher the intracellular concentration of the antibody when the antigen is injected the more severe will be the reaction as if this combination releases some substance from the cells which by its own action produces these symptoms It has been suggested that this substance may be histamine or an allied body (see below)

Diagnosis—The diagnosis of serum sickness does not offer any particular difficulty provided there is a history of the administration of serum a short time previously *It may be confused with measles scarlet fever meningitis* and sometimes with nephritis The pruritus is of great importance in differentiating the skin rashes from specific exanthemata, particularly when the administration of epinephrin gives temporary relief

Course—The disease usually lasts from a few hours to a week and as already mentioned relapses may occur Recovery is the rule

Treatment—The best treatment is prevention This is not always possible in its entirety When it is proposed to give a serum for therapeutic reasons it is well to determine if the patient is sensitive and to what degree This can be done by the intradermal injection of minute but graded amounts into the skin If the patient is sensitive a small amount of the serum is injected subcutaneously with the hope that desensitization may be accomplished with a minimal reaction It is true that this may not be successful but when a serum *reaction should be avoided it may be tried The active treatment is* symptomatic Calcium (see below) histaminase benadryl pyribenzamine and other antihistamine drugs have all been used with equivocal results The pruritus may be temporarily relieved by calamine lotion sodium bicarbonate baths or injections of epinephrine There are indications that the use of salicylates before the eruption appears may prevent or mitigate it and this is claimed to be due to the action of these drugs in preventing or limiting the production of precipitins

Serum Shock

Synonym—Anaphylactic shock, serum accidents

Definition—An explosive and frequently fatal reaction which may immediately follow the intravenous administration of horse serum

Etiology—This condition occurs particularly in those who through their proximity to horses have become subject to asthma or paroxysmal rhinitis, and also in persons who have had a previous injection of horse serum In the former the symptoms are as a rule much more severe than in the latter These accidents or reactions are considered to be anaphylactic in the true sense The similarity to experimental anaphylactic shock is particularly striking in those who have received, weeks, months or even years previously, an injection of horse serum when the symptoms are precipitated by a subsequent injection The relation of serum shock to serum sickness would seem to be one of degree rather than of a different order The antigen must be injected intravenously to produce serum shock in its full intensity It is true that the injection of large amounts of antigen by the subcutaneous or intramuscular routes may produce immediate reactions, but these are usually comparatively mild

Symptoms—The onset is immediate, often occurring before the needle has been withdrawn from the vein There is first a feeling of intense apprehension with almost coincident urticaria edema of the face and extremities and sometimes of the whole body There are also sneezing, a burning sensation in the throat, choking, cough, frothy sputum, and respiratory obstruction causing severe dyspnea and cyanosis Signs of collapse such as dilatation of the pupils rapid, thready pulse falling blood pressure, mental confusion, and frequently convulsions rapidly develop Pyrexia may follow There is an almost immediate disappearance of the leucocytes from the circulating blood and other changes in the blood which will be mentioned below in *the discussion of* traumatic shock Death sometimes is almost instantaneous or symptoms may be delayed for some minutes even to half an hour The cases that are most likely to be fatal are those giving a history of horse asthma or rhinitis When death does not occur the symptoms of serum disease may develop shortly or after a few days

Treatment—*Prophylaxis*—The prevention of these untoward accidents depends upon the recognition of those patients who are hypersensitive and their desensitization Therefore all patients to whom serum is to be given particularly intravenously should be questioned as to familial or personal history of other allergic phenomena such as hay fever asthma or urticaria and also as to whether the patient has had previous inoculations of protective sera If any of these points are elicited the person should be tested by an intracutaneous injection of 0 1 c c of one in ten solution of horse serum If there is a positive local reaction it will then be necessary to carry out desensitization If the skin reaction is strongly positive the first desensitizing dose of 0 025 c c of horse serum should be given subcutaneously and at half hourly intervals it is doubled until 1 c c is given If no severe reaction has occurred the first intravenous dose of 0 1 c c of serum in 5 c c of saline is then administered Every twenty minutes this amount is doubled until full doses are given The specific protective serum to be administered may be employed for this intravenous desensitization If the serum is to be given intraspinally, the same precautions for desensitization must be carried out If the intracutaneous reaction is slight the procedure outlined above may be hastened by giving larger desensitizing doses

On all occasions when intravenous protective sera are to be given, a hypodermic syringe containing 1 c c of epinephrin should be at hand for immediate use in case of the slightest suggestion of a reaction If it be severe, several injections at intervals of a few minutes should be given in fact 2 c c may be given at one dose in urgent cases

ALLERGY

With serum sickness as a background, it now seems proper to discuss the relations of what are generally called clinical allergic reactions to anaphylaxis Are they identical are they related, or are they quite independent phenomena? An exploration into these matters will soon lead us into a maze of truths, half truths and speculations but there are certain points which should be appreciated In the first place the symptomatology of serum sickness and combinations of specific clinical allergic reactions have a striking similarity and in addition there is a common feature in both conditions The most important manifestations of the allergic reactions are found in the sensitiveness of the skin and mucous membranes to this specific form of stimulation and also a tendency to produce contraction of smooth muscle as found in the bronchial tree and gastrointestinal tract These reactions occur both in individuals who have been artificially sensitized to horse serum and in those who develop allergic phenomena such as asthma, but in the latter precipitins and smooth muscle sensitizing bodies cannot be demonstrated Therefore it is only the outward similarity of these phenomena which appear analogous It would be much easier if we could accept the conclusion that the two processes are identical but whereas serum sickness may be produced by any foreign protein, it cannot be accomplished by focal or strictly chemical means of a non protein nature Therefore the identity of these two reactions must still be considered not proved

The allergic patterns as they occur in man have certain common features although these may be modified in degree by the tissues in which they occur They may be of the following nature (1) edematous (2) hyperemic (3) hypersecretory (4) exudative (5) hemorrhagic This general order of reactions occurs in part or in the whole in the skin mucous membrane of the nose nasopharynx and accessory sinuses the larynx trachea and bronchi or the mucous membrane of the gastrointestinal tract There is little proof that it may occur in other viscera except probably in paroxysmal hemoglobinuria It has been suggested that allergy plays a part in certain progressive visceral lesions such as cirrhosis of the liver chronic nephritis and rheumatic heart disease At present these latter are in the realm of being not proved although there are a number of points that make the idea intriguing The association of certain cases of migraine headache focal and general epilepsy vasomotor disturbances and the presence in some of these of known allergic phenomena has opened up a field of investigation which is well worth pursuing and may be taken as suggestive that visceral allergy can occur The differences in the tissue responses as for instance in the type of secretion in bronchial asthma and in paroxysmal rhinorrhea are not dependent upon any modification of the fundamental reaction but rather are due to the essential differences of the

secretory product of these two mucous membranes The more intense the allergic response the more likely is it to approach an exudative and hemorrhagic lesion The great majority of allergic manifestations are usually confined to the first three, namely, edema, hyperemia, and hypersecretion

Before proceeding further it would be well to review some of the general causes that may produce this condition It must be remembered that the specific serum sickness is due to proteins alone, but this does not apply to clinical allergy in general The forces which differ most from pure proteins are physical agents such as heat, cold, light, and cutaneous friction Between these two groups there are a great number of substances such as foods including fish meat, vegetables, fruits, and grains, epidermal products such as hair dandruff, and feathers, the pollens of plants, trees and grasses, bacteria of all kinds, and finally drugs such as aspirin, quinine, potassium iodide, mustard gas aloes opium morphia acacia sulfonamides, and a host of others of many different orders

There is no proof that the so called sensitiveness of man to this great variety of *stimuli* is due to specific precipitins or other detectable bodies The common factor in them all is their capacity under special individual conditions to produce the reactions outlined above and stimulate smooth muscle We have used "stimuli" in the sense that all contacts with our external environment act as such Reactions to stimulation which are usual in the majority are considered as normal, but if the same stimulation produces an unusual effect it is considered abnormal This difference is not inherent in the stimulus but in the reaction of the organism to it It is true that the intensity or amount of the stimulus may modify the reaction in the individual, but this is a quantitative response and in average individuals would be more or less of the same order as for instance a slight degree of heat applied to the skin would produce a mild and fleeting erythema while a similar stimulus of sufficiently great intensity would lead to tissue necrosis This establishes the difference between a beneficent stimulation and a tissue insult Similarly ¼ grain of morphia given hypodermically produces what we call a physiological or pharmacological effect of the drug but 14 grains similarly administered would be poisonous and produce a toxic effect Therefore in the interpretation of allergic reactions we are taking into consideration not so much the intensity or character of the stimulation but whether the stimulated person responds in an abnormal fashion or in a manner that would indicate that a mild or physiological stimulus produces an insult or toxic effect In seeking some explanation of this sensitiveness to external stimuli a search naturally has been made for some substance which being present normally in the system might be released in large quantities or to which an individual might be sensitive even in normal amounts a substance also which when administered in large or toxic amounts would induce phenomena similar to those of serum sickness serum shock or the less specific allergic reactions

Detection of Allergy

When a patient presents symptoms which would suggest an allergic reaction (such as are presently to be described) the family history should be

thoroughly inquired into for any similar familial tendencies Also there should be a close inquiry into any conditions or associations with which these reactions may be related A host of leads must be followed, such as indisposition or dyspepsia following certain foods, or occurrence of symptoms when near animals, such as cats, dogs horses household articles such as pillows or bedding, the period of the day or year when the attacks are most common, exposure to cold heat, light or friction the presence of flowers in the house the taking of drugs, particularly analgesics and hypnotics Often the detective work is comparatively simple, as for instance a history of a person who always has an attack of rhinorrhea or asthma at three o clock in the morning would naturally suggest that it is caused by or at least associated with, the bedding It might be feather pillows woolen blankets or a horsehair mattress Some may not be able to abide the presence of a cat others are prevented from eating buckwheat honey shellfish strawberries or pork Again there are those who claim they cannot take a cold bath, as immediately afterward they are afflicted with hives urticaria, or violent attacks of sneezing or dyspnea, and even syncope The presence of any focus of infection, particularly in the respiratory passages should be carefully sought for Out of such a searching history definite leads frequently develop The next step is to determine whether the individual is skin sensitive to any of these conditions or substances This is done by either the scratch method intradermal method or patch test

Scratch Method—The superficial layers of the skin over a tiny area are removed by a needle or other sharp instrument Serum is not to be drawn and a small amount of the allergen, either dry or in solution, is then applied This is repeated with as many substances as have been suggested by the history

In the **intradermal method** a small amount 0 01 to 0 02 c c of a sterile solution of the allergen is injected into, but not under the skin

The **patch test** is particularly applicable for those substances which produce a so called dermatitis such as poison ivy nettles talcum powder dusting powder personal clothing (silk cotton linen or wool etc) A small amount of the suspected material or an extract thereof upon a piece of blotting paper is applied to the skin and held in place by a piece of adhesive plaster A reaction similar to the dermatitis will be produced if the patient is sensitive

The reactions to all these methods may be either immediate or delayed The former develops within five or ten minutes and assumes the form of a wheal which may be itchy The reason for this immediate reaction is not known but it strongly resembles the local reactions due to histamine However it has been found in these cases that a circulating skin sensitizing anti body' can be demonstrated in the serum by passive transfer The delayed reaction may occur after some hours or even several days and would appear to be similar to the response in serum sickness

Ophthalmic tests have been advocated from time to time but are not without danger They are done by introducing into the conjunctival sac a small amount of solution of the suspected allergen In about five minutes there are conjunctival redness swelling itchiness and lacrimation

Urticaria

Synonym—Angioneurotic edema

Definition—Urticaria is a term applied to a superficial localized edematous condition of the skin which is intensely itchy, while angioneurotic edema is reserved for deeper or subcutaneous areas In both conditions there are redness of the skin, and an intense pruritis They are commonly known as "hives" For many years it was considered a neurosis, but now there is no doubt that it is a definite allergic reaction These swellings may occur on the mucous membrane of the mouth, pharynx, larynx, and have been detected in the esophagus and the mucous membrane of the gastrointestinal tract



10—Urticaria (Courtesy of Dr Otto Leslie Castle From Sutton and Sutton Diseases of the Skin)

They are produced by a vast variety of substances such as feathers hair, dusting powders house dust etc, but probably the most important are foods such as milk, eggs, peas, beans shellfish and also many drugs The list is almost interminable Such persons are frequently sensitive to many substances The skin tests are not satisfactory in these cases and to detect the cause one must frequently resort to a process of elimination or in other words, trial and error

Treatment—The immediate treatment consists of the application of soothing lotions, and a hypodermic injection of 0 5 c c of epinephrin This usually brings about some relief but the condition soon returns unless the primary cause can be eliminated It may be present constantly if the cause is constant, or intermittent if the stimulus is present on relatively rare occasions as when shellfish or strawberries are eaten or when aspirin quinine, or the coal tar products are taken as analgesics or hypnotics Specific treatment is the same as for hay fever

Hay Fever

Synonyms—Allergic coryza, rose fever paroxysmal rhinorrhea, paroxysmal rhinitis, vasomotor rhinitis, and pollinosis

Definition.—This is an allergic condition of the mucous membrane of the nose, conjunctiva, and upper respiratory tract It is usually due to the inhalation of pollens, but may be caused by emanations from other substances and by foods

Symptoms—When due to pollens there is usually a definite seasonal incidence This will vary according to the latitude at which the individual is living In the spring of the year it is frequently associated with the pollen of trees such as the alder hickory oak ash elm and poplar, while in the summer it is most frequently due to the pollen of flowers and grasses as the rose and hay Toward the autumn many cases are due to the pollen from ragweed and buckwheat It may be present *intermittently throughout the whole year* if the flower, the pollen to which the individual is sensitive is brought into the house

Local infections of the accessory sinuses may also produce a similar reaction and under these conditions the seasonal periodicity will not be conspicuous but the reaction will be intermittent, occurring throughout the year There is a swelling of the mucous membrane with hyperemia and hypersecretion and these vary greatly in intensity from a mild coryza to an intense rhinorrhea and lacrimation The mucous secretions contain many eosinophiles and there is often an eosinophilia There is a sense of burning and paroxysms of sneezing are most distressing Nasal obstruction occurs, due to the swelling of the mucous membrane As in all forms of allergy, hay fever may not occur alone but may be associated with asthma urticaria and eczema These conditions may appear in sequence or any of them may be present at the same time

Diagnosis—The diagnosis of hay fever as such offers little difficulty but the cause may be extremely elusive It is only by continuing to seek for this, and removing or avoiding it that an eventual cure can be hoped for It would serve no useful purpose to enumerate the possible causative agents

Course—The course usually follows a seasonal repetition unless a complete diagnosis is made and the cause is removed or the individual is desensitized Many cases can be relieved and a permanent cure can be effected in a certain number

Treatment—Although the cause may not be found often by repeated trials patients find a district in which they are completely free of symptoms but one patient who finds his freedom in the mountains may not at the sea shore and in another it might be the reverse Therefore each victim must try to find his own salvation Certain districts are supposed to be comparatively free of hay fever due to ragweed and goldenrod such as northern Maine New Brunswick Nova Scotia and the Province of Quebec north of the St Lawrence also the White Mountains and southern California but it is interesting to note that ragweed is not necessarily absent in these localities

Specific Treatment—If the proper pollen can be determined, vaccination against the cause is sometimes successful This is accomplished by giving minimal injections of the pollen extract in increasing amounts, beginning some ten to twelve weeks before the expected onset of the disease The amount to be given will depend upon the sensitiveness of the individual The greater this is, the smaller should be the initial injections One should not be too optimistic as to the results Asthma due to pollen is usually *greatly* benefited, but for hay fever the results are not as *good*, and at best are temporary after one course of treatment If the patient should seek relief immediately before an attack is expected or during one, it is well worth while to give a series of inoculations but these should be of very small amounts The best method of specific treatment is to continue the inoculations throughout the year giving an injection every two to three weeks and with the maximal amount that the patient can tolerate without producing a reaction Drugs are of little value except as palliatives The most popular are ephedrin and epinephrin sprays which not only reduce the edema and hyperemia but also control the hypersecretion Cocaine is also popular but should never be advised except in the most desperate cases on account of the liability of establishing a habit

It has been mentioned above that histamine or a histamine like substance may play an important role in allergic reactions It was thought therefore that histaminase might be effective in many of these conditions This however has not been borne out by experience On the other hand many so called antihistamine substances have been introduced into our armamentarium At the present there are some thirty two or more of these of which benadryl and pyribenzamine are examples One cannot be too dogmatic as to their usefulness Many cases of hay fever and urticaria seem to be benefited in a more or less striking degree while in others they fail entirely Furthermore there cannot be claimed to be a constant specificity for any one of them in a particular type of reaction

Vasomotor Rhinitis (Perennial Coryza)

This is in every way identical with hay fever except that the condition persists either continuously or intermittently throughout the year and is therefore not due to pollens The most common causes are infections of the upper respiratory tract or air borne dusts from animals birds cereals fabrics, grains tobacco or other substances Another group of causes comprises foods and drugs and it is sometimes difficult to be certain whether these exert their effect during the time they are in the mouth or through absorption from the gastrointestinal tract Those producing this result have already been mentioned under the general causes of allergy Definite anatomical changes are present in these chronic conditions either of the mucous membrane of the nose and nasopharynx, or in the accessory sinuses Histological examination will show edema and infiltration with many small round cells and eosinophiles It has commonly been called infective rhinitis and an infectious background is undoubtedly often present

Diagnosis —The diagnosis of these conditions is seldom difficult, but the cause is often more elusive than in the case of frank hay fever The treatment is similar although the aid of a rhinologist to treat the local anatomical condition is often of great advantage Autogenous vaccines, if the infecting organism can be determined sometimes give good results, especially when there is also asthma

Asthma

Definition —Asthma consists of acute paroxysmal or more prolonged attacks of dyspnea due to bronchial and bronchiolar respiratory obstruction

Etiology —It is a clear cut anaphylactic reaction in the respiratory mucous membrane, and is characterized by edema hyperemia hypersecretion and exudation and contraction of the circular bronchial muscles It may be caused by hypersensitivity to the many substances mentioned in the early parts of this chapter Familial indications of allergy are common in these people as well as a personal history of other forms of allergy in past years

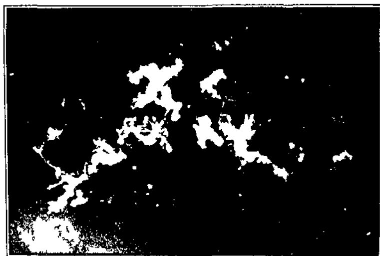


Fig 11 —Photograph of bronchial plugs expectorated in a case of asthma Compare with Fig 40

Symptoms —In the acute type the onset is explosive As soon as the individual is exposed to the precipitating factor there is rapid onset of dyspnea which may be so severe with deep purple cyanosis as to suggest acute suffocation The extraordinary muscles of respiration are brought into play and are assisted by the individual s grasping some firm object Inspiration is an obviously forcible act and expiration is conspicuously prolonged In a short time the thorax approaches the position of full inspiration the reason being that the act of inspiration is more effective than the more passive expiration In the early stages the respiratory volume is increased but as the minutes pass the lungs may be so distended and the inspiratory effort so ineffectual that it declines in amount Unless this condition is relieved unconsciousness with muscular twitches and then convulsions probably due to intense anoxemia may result All paroxysms are not as severe

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It has been mentioned above that histamine or a histamine-like substance may play an important role in allergic reactions. It was thought therefore that histaminase might be effective in many of these conditions. This however has not been borne out by experience. On the other hand many so-called antihistamine substances have been introduced into our armamentarium. At the present there are some thirty two or more of these of which benadryl and pyribenzamine are examples. One cannot be too dogmatic as to their usefulness. Many cases of hay fever and urticaria seem to be benefited in a more or less striking degree while in others they fail entirely. Furthermore there cannot be claimed to be a constant specificity for any one of them in a particular type of reaction.

Vasomotor Rhinitis (Perennial Coryza)

This is in every way identical with hay fever except that the condition persists either continuously or intermittently throughout the year, and is therefore not due to pollens. The most common causes are infections of the upper respiratory tract or air borne dusts from animals, birds, cereals, fabrics, grains, tobacco or other substances. Another group of causes comprises foods and drugs, and it is sometimes difficult to be certain whether these exert their effect during the time they are in the mouth or through absorption from the gastrointestinal tract. Those producing this result have already been mentioned under the general causes of allergy. Definite anatomical changes are present in these chronic conditions either of the mucous membrane of the nose and nasopharynx, or in the accessory sinuses. Histological examination will show edema and infiltration with many small round cells and eosinophiles. It has commonly been called "infective rhinitis" and an infectious background is undoubtedly often present.

fact in many cases of asthma an allergic basis cannot be established but on psychological exploration a definite psychosomatic pattern can be revealed

Pathological Anatomy—*The anatomical changes in persons who have* died of an acute paroxysmal asthmatic attack are similar to those dying of a serum accident or anaphylactic shock There are intense pulmonary emphysema edema of the lungs and other tissues, and cardiac dilatation, and in addition the ordinary signs of asphyxia In chronic asthma the emphysema is anatomical and permanent There are hypertrophy and dilatation of the heart, particularly the right ventricle the mucous membrane of the bronchi and bronchioles is thickened and edematous and there is evidence of a productive lesion in the submucosa with eosinophilic infiltration The bronchial tree may be completely plugged with a tenacious exudate The nasal nasopharyngeal and paranasal sinuses may show a productive lesion similar to that found in the nonseasonal hay fever Indeed, chronic rhinitis and sinusitis are commonly associated with asthma

Course—In long standing cases of asthma anatomical bronchial and pulmonary changes frequently develop There are permanent emphysema and signs of chronic bronchitis, and if there should have been one or more attacks of lobar or bronchopneumonia atelectasis and bronchiectasis may be found In other words the functional allergic condition may become insignificant compared to the permanent anatomical changes Death from asthma is not common but when it does occur it is usually due to suffocation from the numerous bronchial plugs or to circulatory collapse from anoxemia It is well to be cautious in proceeding with nose and throat operations for the removal of foci of infections or polypi during the time when a patient is suffering acutely from the disease There may be precipitated a most violent and often fatal status asthmaticus' leading to suffocation and collapse

Diagnosis—The diagnosis of an acute attack of asthma presents little difficulty The first episode may be confused with bronchiolitis or severe bronchitis but the numerous dry rales and the obvious interference with respiration are quite distinctive In the more chronic cases chronic bronchitis emphysema and sometimes bronchiectasis make it difficult to assess how much of the symptomatology is due to these and how much to asthma In time the asthmatic features may disappear Acute right ventricular cardiac failure may also confuse the picture as this is not an unusual sequela to long standing asthma In these cases it is important to appreciate that the cardiac factor may be of greater importance than the asthma Rarer conditions to be differentiated are bronchial obstruction from bronchogenic carcinoma or mediastinal tumors

Treatment—The treatment of the immediate attack is best accomplished by *giving 0 5 to 1 c c (7 to 15 minims) of a 1 1 000 solution of epinephrin subcutaneously* This usually gives prompt relief and it can be repeated as often as required Some have advocated the repeated use of small doses of ephedrin several times a day to prevent or at least modify the severity of the attacks from their beginning This drug has been disappointing in the treatment of the acute attacks once they have been established *Morphia 1/8 to 1/4 grain hypodermically,*

as this description implies Many of them are comparatively mild, but may follow each other in rapid succession while in other instances there may be long intervals between them There is cough, often associated with expiration, which to some extent aids this act The sputum is usually scanty and tenacious, consisting of thick, viscid mucus which may form a cast of the smaller bronchi, and when expectorated is in the form of branching plugs or spirals (Curschmann's) (see Fig 511) The sputum, in addition to this mucous contains eosinophiles and Charcot Leyden crystals It is rare that this sputum is blood stained although in severe cases a slight tinge may be noted Edema of the lungs sometimes occurs apparently due to the great increase of pressure in the pulmonary circulation Then the sputum becomes frothy and copious and may be frankly pink in color A careful examination of the sputum by the physician may provide him with valuable information In uncomplicated asthma this is composed entirely of mucus without any gross evidence of a purulent component If this be present, it indicates an infective factor which may be primary or secondary and has an important bearing on the course and handling of the case Pain is not a prominent symptom, but after a severe attack there may be soreness in the intercostal spaces and in the epigastrium, probably due to the violent muscular effort which has been exerted

During the early stages of an attack when the volume of pulmonary ventilation is increased there is a lowering of the alveolar CO and an acute uncompensated gaseous alkalosis may result with alkaline urine and tetany In the later stages a CO_2 retention may occur The first stage is important because if prompt relief is given and the cyanosis rapidly relieved there may be long periods of apnea, and frequently periods of Cheyne Stokes breathing

The physical signs are quite characteristic and consist of numerous bilateral dry râles of all sizes They are audible without a stethoscope and can be palpated In addition the percussion note is hyperresonant due to a transitory overdistention of the alveoli The cardiac dullness may be obliterated and the heart sounds distant with accentuation of the second pulmonic sound In the blood there is often found a slight leucocytosis due to an eosinophilia

The cause of the symptoms and signs is the irregular narrowing of the lumina of the bronchi and bronchioles due to swelling of the mucous membrane and contraction of the circular muscles This as already mentioned is a purely allergic effect The eosinophiles and Charcot Leyden crystals in the sputum and the eosinophilia are also indicative of this

The precipitation of an attack is due to exposure to the specific causative agent but this susceptibility may be enhanced by mental or psychic stimulation physical exertion exposure to cold or heat irritating gases or atmospheres, sexual excitement and a host of other external or environmental stimuli In other words there are again to be found the two possible factors the susceptibility to a specific substance and the increase of this susceptibility by nonspecific conditions

At one time asthma was considered as a purely neurotic condition With the introduction of the allergic concept the emotional factors were almost completely neglected There has now however been a return to a broader concept which may be applied to many so called allergic phenomena In

to the direct action of foodstuffs upon the gastrointestinal mucous membrane as in the contact dermatitis Gastric hemorrhages of an allergic origin have also been described The sequence of events in these cases is not always clear but it is well to bear the possibility in mind The similarity of mucous colitis and bronchial asthma has already been referred to (see Chapter X)

Physical Allergy

It is not infrequent that one is consulted by patients who claim that on exposure to cold they develop a syndrome which from its description strongly suggests an allergic reaction For instance, when the hands are immersed in cold water urticaria develops, and it will frequently be found if cold water or a piece of ice is placed on some other portion of the skin, urticaria will develop over the localized area of its contact Some persons are so sensitive that they cannot take a cold bath as following this the urticaria is diffuse and *collapse symptoms may occur Similarly exposure to cold air although the* body is covered, may produce an attack of asthma or acute rhinorrhea Others on swallowing cold drinks or foodstuffs, as ice cream, may also develop acute prostration, tremors, asthma, urticaria, or other allergic phenomena

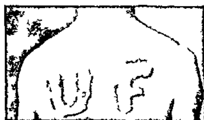


Fig 51 —Urticaria hiemalis (the type due to cold) The area of edema does not extend beyond the area directly exposed to ice (Courtesy of Dr W W Duke. From Sutton and Sutton Diseases of the Skin.)

There is also a group of persons who respond to the opposite thermal insult namely, when they are exposed to hot weather drink hot liquids or eat hot foods, they have similar reactions The more difficult ones to isolate are those who are so sensitive that the warmth produced by mental, physical sexual or psychic excitement precipitates an attack

Persons who are sensitive to the solar spectrum also compose an interesting group It does not follow that every case is sensitive to the same wave lengths which may add to the confusion but there are people who when exposed to sunshine develop urticaria dermatosis even dermatitis and sometimes alarming collapse

It is these cases of physical allergy which are hard to explain upon the usual precipitin basis and they would point much more directly to some histamine or histamine like reaction

Paroxysmal Hemoglobinuria

Closely associated with the allergic reactions due to cold is paroxysmal hemoglobinuria This apparently results from the production of a hemolysin

is of value in mild cases but should be given with great caution as it may relieve distress but hasten respiratory failure Tincture of stramonium with potassium iodide has been a favorite remedy, and in many cases gives relief, particularly when taken over prolonged periods Ipecacuanha is of particular benefit in children, as it assists them through the act of vomiting, in ridding the trachea and upper bronchi of the tenacious mucus Belladonna and atropin have little antispasmodic effects in these cases Trasentine sometimes gives prompt relief What was written concerning antihistamine drugs under Hay Fever is equally applicable to asthma It may be stated, however that benadryl has a certain advantage in addition to this action namely a sedative effect which indicates it may be given at bedtime and during the night to assist in obtaining a restful sleep which is often a problem difficult to solve

The general handling of the case is important All the normal functions should be maintained with regularity, and the diet carefully scrutinized for any possible allergic susceptibility The specific treatment is both prophylactic and curative If the cause can be ascertained, the patients must by all means be kept from its contact Inoculations as in other forms of allergy should be undertaken to reduce the sensitivity of the individual The treatment of asthma due to infectious or focal lesions, particularly in the upper respiratory tract is fraught with great difficulty Autogenous vaccines have been advocated and appear to be of value if reactions are produced, but on the other hand almost equally good results have been obtained from producing similar reactions by nonspecific proteins The removal of focal infections in the upper respiratory tract should be undertaken with great caution It has already been mentioned how there may be alarming and even fatal results from these procedures if undertaken at the improper time When these occur epinephrin should not be spared In fact in the most desperate cases a continuous intravenous injection of saline at the rate of 2 c c per minute to which a minim of epinephrin is added every three to five minutes may tide the patient over an almost hopeless collapse The amount given can be controlled by the changes in blood pressure which at the beginning will be found to be low It should not be raised above 130 mm Hg systolic pressure For respiratory distress and cyanosis air enriched with oxygen or a mixture of helium and oxygen should be inhaled constantly with a proper apparatus (see Fig 63) until these symptoms are relieved The treatment of the sequelae of asthma such as chronic bronchitis emphysema and bronchiectasis is discussed elsewhere

Gastrointestinal Allergy

There have been reported groups of cases presenting acute abdominal pain vomiting, diarrhea and collapse relieved by epinephrin These symptoms have frequently been associated with vasomotor rhinitis urticaria, angioneurotic edema hay fever or asthma Such symptoms occurring in one who is known to be allergic should be suspected as being due to this cause or in cases where no other explanation can be found, it is profitable to explore this avenue for a possible etiology It is supposed that these attacks can be initiated in exactly the same manner as asthma or hay fever, or may be due

to the direct action of foodstuffs upon the gastrointestinal mucous membrane as in the contact dermatitis Gastric hemorrhages of an allergic origin have also been described The sequence of events in these cases is not always clear, but it is well to bear the possibility in mind The similarity of mucous colitis and bronchial asthma has already been referred to (see Chapter X)

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It is not infrequent that one is consulted by patients who claim that on exposure to cold they develop a syndrome which from its description strongly suggests an allergic reaction For instance, when the hands are immersed in cold water urticaria develops, and it will frequently be found if cold water or a piece of ice is placed on some other portion of the skin, urticaria will develop over the localized area of its contact Some persons are so sensitive that they cannot take a cold bath, as following this the urticaria is diffuse and collapse symptoms may occur Similarly exposure to cold air although the body is covered, may produce an attack of asthma or acute rhinorrhea Others on swallowing cold drinks or foodstuffs, as ice cream may also develop acute prostration, tremors, asthma urticaria, or other allergic phenomena



Fig 51 —Urticaria (localized) the type due to cold The area of edema does not extend beyond the area directly exposed to ice (Courtesy of Dr W W Duke From Sutton and Sutton Diseases of the Skin.)

There is also a group of persons who respond to the opposite thermal insult namely when they are exposed to hot weather drink hot liquids or eat hot foods they have similar reactions The more difficult ones to isolate are those who *are so sensitive that the warmth produced by mental physical sexual* or psychic excitement precipitates an attack

Persons who are sensitive to the solar spectrum also compose an interesting group It does not follow that every case is sensitive to the same wave lengths which may add to the confusion but there are people who when exposed to sunshine develop urticaria dermatosis even dermatitis and sometimes alarming collapse

It is these cases of physical allergy which are hard to explain upon the usual precipitin basis and they would point much more directly to some histamine or histamine like reaction

Paroxysmal Hemoglobinuria

Closely associated with the allergic reactions due to cold is paroxysmal hemoglobinuria This apparently results from the production of a hemolysin

when the patient is exposed to a certain temperature In addition to the appearance of a "bloody urine" (really hemoglobinuria) there may be pyrexia, shivering, malaise, and headache, and sometimes collapse The attacks may be initiated either by submerging part of the cutaneous surfaces, such as the hands in cold water or taking a cold bath This type is called "hemoglobinuria e frigore" and it is only in such cases that the Donath Landsteiner reaction is positive Sympathectomy has been advocated as a therapeutic measure The exact manner of production of the hemolysin is not understood It is a striking feature however, that practically all of the cases reported have either given a positive Wassermann reaction, or anatomical evidence of syphilis There are other types, namely, hemoglobinuria on exertion nocturnal hemoglobinuria associated with hemolytic anemia, and paralytic hemoglobinuria when the pigment is methemoglobin associated with paralysis of the skeletal muscles

Miscellaneous Allergic Reactions

It would not be within our province to cover in detail all the conditions that have been ascribed as possibly due to allergy There is however, one large group which, in addition to urticaria and angioneurotic edema, may assume a variety of dermatological patterns, such as eczema erythemas, pruritus prurigo lichen purpura pompholyx etc Purpura of the Henoch type has been accused of having an allergic basis Finally there are those who suffer from migraine of unexplained origin Many of these give a familial and personal history of allergy, and intimately related to these are cases of idiopathic epilepsy Before a case of epilepsy is finally pronounced idiopathic, the possibility of its having an allergic foundation should be explored

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CHAPTER XXII

DISEASES DUE TO ABNORMAL ENVIRONMENTS

INTRODUCTION

Through the vicissitudes of life the human body is called upon from time to time to cope with environmental conditions which cannot be considered a usual when compared with its normal or average surroundings The principal physical changes of environment are those of temperature and barometric pressure The human body has the facility of accommodating itself to wide variations in these conditions In addition the respired air may be deficient in its most important constituent—oxygen—or may contain harmful gases and other substances Even to many of these conditions the body may develop a certain degree of protection particularly if it is exposed to them gradually or can get rid of them with greater facility than they are absorbed The results of harmful changes of environment can hardly be called diseases al though they may produce death They are rather changes in the physico chemical relationships in the body to which it cannot adapt itself with sufficient rapidity Whereas some of them, like exposure to intense heat and cold have been overcome in great measure by modern knowledge others which a century ago were not conceived as possible such as diving to the depths of the sea and climbing close to the stratosphere are now matters of everyday occurrence These adventures have enlightened us as to what the animal organism can do in accommodation, and have also taught us means of pre venting their deleterious effects

EFFECTS OF HEAT

The response of the human organism to an increase of its thermal en vironment depends upon a number of factors in addition to the actual level of the thermometer There must be considered the degree of humidity and the movement of air currents or cooling power of the atmosphere in which the body is immersed If the temperature of the environment is equal to or greater than 98° F heat loss cannot be accomplished by radiation and conduction but is assisted by evaporation of water by sweating and increased pulmonary ventilation The former is assisted by active air currents either naturally by winds or artificially by fans If the atmosphere is saturated with aqueous vapor this evaporation cannot take place and it has been determined by Haldane that at rest in such a saturated atmosphere the body temperature of man increases per hour one degree at 89° F two degrees at 94° F and four degrees at 98° F With physical exertion under similar environmental conditions a proportionate increase of body temperature will occur depending upon the increase of oxygen consumption In general any of these conditions or a combination of them which lead to retention of heat will raise the body

temperature The clinical response to this change in the internal environment varies considerably in different people and may produce somewhat different symptom patterns Conditions which increase the response or susceptibility are old age, fatigue, alcoholism obesity, and circulatory diseases Exposure over periods of time may bring about a certain tolerance Loss of water and sodium chloride through sweating also may modify the effects, particularly if at the same time there is a copious intake of water The tissues become hypotonic through loss of salt which is not replaced This produces "water poisoning" which will be considered below (see Heat Cramps)

I **Moderate Pyrexia (Heat Retention)** —When the body temperature rises several degrees there are a throbbing headache tachycardia dyspnea and restlessness Sweating decreases and there is a polyuria This is one of the dangers in hyperthermic therapy

II **Heat Cramps (Water Poisoning)** —This is due to a hypotonic state of the body owing to a relative increase in sodium chloride loss through the sweat There may indeed be a concentration of the blood and a diminished blood volume It usually occurs in stokeholds deep mines and other hot environments It is characterized by muscular twitchings and cramps abdominal colic nausea vomiting and diarrhea Respiration may be embarrassed through intercostal and diaphragmatic spasms It closely simulates a mild form of tetany It is aggravated by drinking water beer or other liquids The experienced workers have learned or it has been handed down by tradition certain prophylactic measures such as the custom of miners in deep hot mines of taking into the pit a mixture of oatmeal and salt which they munch during their work or as stevedores and rolling mill workers liberally add salt to their beer Likewise the condition is promptly relieved by the intravenous injection of a liter of hypertonic (1 5 per cent) salt solution

III **Heat Exhaustion** —If heat retention exceeds a moderate degree the symptoms all become much aggravated Sweating ceases and the skin becomes cold damp and pale but the rectal temperature is increased although the mouth readings may be normal and the axillary temperature decreased In addition to the symptoms mentioned in I above there are pronounced nervous manifestations—vertigo ataxia visual impairment dilated pupils and great exhaustion The treatment consists of rest and cool surroundings

IV **Sunstroke (Hyperpyrexia Heat Stroke Insolation)** —This is a further manifestation of heat retention The heat control seems to be suddenly lost and a mounting hyperpyrexia develops Headache and signs of mild heat retention may be premonitory but the onset is often a sudden collapse with delirium followed by unconsciousness and coma The skin instead of being cool and damp is hot and dry the pupils are contracted tachycardia is 170 to 190 respirations are deep almost of the type caused by acidosis and periodic breathing is the rule in the most severe cases The rectal temperature may show readings of 106° to 110 F Purpura often occurs and there is complete flaccidity although in the early stages muscular twitchings and cramps as in II may be detected This condition has a high mortality and accounts for the frequent deaths in the heat waves recorded each summer

The treatment consists of maintaining the skin circulation by constant friction and promoting heat loss at the same time by playing a spray of cold water over the whole body in the presence of air currents produced by fans Cold packs with sheets may be substituted for the spray Friction of the skin by sponges or gauze pads should be continuously employed It is most important that surface vasoconstriction should not occur Experienced stokers have known a homely prophylactic measure, which consists in wearing a heavy flannel shirt saturated with sweat and water, which perpetuates the cooling effect of evaporation, and simulates the water skins hung in the open air in hot desert regions Ice packs and ice baths, formerly used lead to vasoconstriction of the cutaneous vessels, and thus reduce heat loss and raise the visceral temperature

The body temperature should not be reduced below 102° F, for secondary hypopyrexia may be induced by too rapid heat loss Dehydration and salt loss should not be neglected They may be corrected by intravenous hypertonic saline injections A moderate pyrexia may persist for several days, but after 36 hours of temperature control recovery is the rule Mental symptoms may persist for some days or weeks, and headaches may be distressing for many months A person once the victim of heat stroke may for years become restless and apprehensive with a mounting thermometer It is difficult to be certain how much of this is due to fear and how much is a residue of the thermal shock or a hypersensitiveness to heat (see Heat Allergy)

EFFECTS OF COLD

Exposure to a moderate degree of cold stimulates the oxygen consumption and thus raises the basal metabolism in this environment This has been found to be constant in people who live in the arctic regions as compared with those in the temperate zones and theirs is again higher than that of inhabitants of the tropics But this is a physiological response to a normal environment, and the heat loss would be easily regulated From 70 to 80 per cent of heat loss occurs through the skin and this is accelerated as the surface temperature is reduced Compensation is brought about by constriction of the skin vessels, thus causing less blood to be brought to the surface for cooling while shivering and increased muscle tonus produce more heat Thus there are reduced heat loss and increased production If however this compensation is not effective and the body temperature of a warm blooded animal falls below 68° F death is certain Even at higher temperatures the outcome is dubious The lowest temperature recorded in man with recovery is 75° F

All people are not equally susceptible Infants and the elderly are particularly so while the virile and more robust particularly the well nourished are much less affected The most important predisposing factors to pathological lowering of the body temperature in a cold environment are inadequate clothing shortage of food muscular fatigue and alcoholism The last acts through producing imperfect nervous thermal control and somnolence

Symptoms—The first symptoms are shivering and increased muscle tone There are mental alertness and a desire for exercise but when the body tem

perature begins to fall, this is followed by muscular fatigue weakness, stiffness and drowsiness with an almost uncontrollable desire to sleep which, if given way to, drifts into coma These all indicate a lowering of heat production as well as a continued heat loss and the oxygen consumption declines as in a cold blooded animal Death eventually occurs

Treatment—The best treatment is absolute rest and elevation of the body temperature by a warm environment This is effected by wrapping the person in warmed blankets in a heated room If these are not available a similar purpose may be attained by keeping the victim in close contact to other persons or animals and protected from the wind Hot water bottles and hot bricks should be used with caution, as the ischemic skin is easily burned Sips of hot beverages at short intervals help to increase the body temperature The person may appear to be alive but irreparable damage has been done and he may die later If not complete recovery occurs

Allergic reaction to cold and local lesions (frostbite) are considered elsewhere

EFFECTS OF HIGH BAROMETRIC PRESSURE

Synonyms—Compressed air illness caisson disease, divers palsy the bends

Etiology—The effects of increased barometric pressure are due not to the pressure itself but to the physical effects this has on the solution of gases in the blood by way of the lungs The ordinary barometric changes met with in our daily life do not produce the effects to be described The solution of gases in a fluid depends upon their partial pressures (Dalton's law) Any increase of these pressures in man s normal environment is negligible, therefore no symptoms are produced

Men working in caissons as in building tunnels and as divers, are exposed to an environment where the barometric pressure may be raised to ten or fifteen atmospheres The oxygen and nitrogen go into solution in the plasma and eventually saturate the tissues in accordance with their partial pressures, therefore at five or eight atmospheres pressure there will be five or eight times as much in solution in these tissues This applies both to oxygen and nitrogen, but in subsequent events the former is readily handled by the hemoglobin and tissues while the nitrogen being a foreign element except at normal pressures causes the symptoms and lesions All tissues do not absorb nitrogen at the same rate nor to the same amounts Fats absorb five times as much as water and therefore take a relatively long time to become saturated Tissues with tardy or limited blood flow such as the ligaments bones spinal white matter liver and spleen come into equilibrium gradually But at the best of times it takes some hours even with the increased circulation rate of physical work for the entire body to come into equilibrium at the new level During this period no symptoms are produced but the duration and amount of pressure determine the degree of saturation of the tissues

As soon as the barometric pressure is reduced the nitrogen in the blood is readily given off into the alveolar air and at the same time nitrogen comes out of solution from the tissues As its absorption and saturation of tissues were

irregular so will be the desaturation Physical exercise will accentuate and localize the effect to the group of muscles or limb which is most used If the decompression is not done properly bubbles of nitrogen will form in the tissues, the capillaries and small veins, and venules This will be particularly prominent in the fat deposits, white matter of the brain and cord and other tissues where the saturation is high or the blood flow is slow These bubbles or air emboli compress or rupture the tissues, particularly where they are most numerous and largest Hemorrhages and obstruction of the blood flow are common

Symptoms —The symptoms in such a widely distributed and irregular disturbance will be variable and bizarre They usually appear an hour or so after the faulty decompression has been completed, although in severe cases a few minutes only may elapse There are pains in the joints muscles and ligaments (hence the bends), abdominal cramps, nausea, vomiting and a great variety of nervous phenomena including dizziness, syncope deafness, paralysis or paresis, particularly of the legs, loss of sensation and more rarely hemiplegia, paraplegia or monoplegia The more rapid the onset, the more serious and widespread are the symptoms, and the more likely is death to occur In these cases pulmonary and coronary emboli and frothy blood in the cardiac chambers may be found Fortunately most cases are comparatively mild The condition is most severe in fat men and even plump men should not be allowed in high pressure caissons

Treatment —The best treatment is prophylaxis which depends upon proper decompression The older method was by gradual but steady reduction of the pressure In 1906 Haldane introduced the method of reducing the pressure in stages It is not only safer but also more rapid He found that rapid decompression of atmospheric pressure from two atmospheres to one could be accomplished without danger Decompression is not safe if the pressure of nitrogen inside the body is much more than twice that of the atmospheric nitrogen Therefore the first step is to reduce rapidly the absolute pressure to one half A time interval is then allowed to elapse during which the body comes into equilibrium The pressure is again reduced by half with another interval and so on down to one atmosphere (normal pressure) The duration of the intervals depends upon the maximum pressure and the duration of the exposure If symptoms appear after the decompression is completed, the person must be immediately recompressed to at least three atmospheres of pressure and the stages repeated with longer intervals

EFFECTS OF LOW BAROMETRIC PRESSURE

The percentage of oxygen in the atmosphere is not the sole factor which affects respiratory function It was mentioned in Effects of High Barometric Pressure that gases are soluble in accordance with their partial pressures This is equally true in regard to the combination of oxygen with hemoglobin and its solubility in the plasma Therefore a lowered oxygen percentage under high barometric pressure may combine with hemoglobin to form oxyhemoglobin in the same amounts as when there are a normal percentage and pressure

It is these factors in the alveolar air which determine the partial pressure of oxygen to which the blood in the capillaries is exposed

In making these calculations allowance must be made for the partial pressure of the aqueous vapor in the alveolar air and in the following examples this will be kept constant at 47 mm Hg

I Normal O_2 percentage with normal pressure

$$\frac{15\% \; O_2 \times (760 \text{ mm} - 47 \text{ mm})}{100} = 106.95 \text{ mm partial pressure } O_2$$

II Low O_2 percentage with high pressure

$$\frac{7\% \; O_2 \times (1500 \text{ mm} - 47 \text{ mm})}{100} = 105 \text{ mm partial pressure } O_2$$

III Normal O_2 percentage with low pressure

$$\frac{15\% \; O_2 \times (380 \text{ mm} - 47 \text{ mm})}{100} = 50 \text{ mm partial pressure } O_2$$

IV Low O_2 percentage with normal pressure

$$\frac{7.5\% \; O_2 \times (760 \text{ mm} - 47 \text{ mm})}{100} = 55 \text{ mm partial pressure } O_2$$

In the present discussion we are concerned with III and IV

Normal oxygen percentage and low barometric pressure (III) is met with in high altitudes aeroplane flights and balloon ascensions Low oxygen percentage and normal barometric pressure (IV) is encountered at times in mines *tunnels wells submarines, etc The net result in both is the same, namely* a reduction in the percentage of oxyhemoglobin in the arterial blood There is one important point always to be taken into consideration—the rate at which the lowering of the partial pressure of O_2 is produced If this be sudden the onset of symptoms is rapid and severe while if it be slower, covering several days or weeks acclimatization usually takes place and this is particularly obvious in persons who have been accustomed to lowered partial pressure

The symptoms are the same under all circumstances the only variation being dependent upon the rapidity of exposure the degree of lowered partial pressure and the susceptibility or acclimatization of the individual They are headache vertigo dyspnea palpitation and cyanosis, particularly on exertion mental *irritability and weakness Hyperpnea is obvious and causes a decreased* alveolar CO_2 percentage There may be only slight nausea but explosive vomiting is characteristic and closely resembles that in seasickness It is commonly stated that epistaxis and bleeding from the ears are features If they occur, they are due to the lowered barometric pressure and not to the reduced oxygen pressure They may occur in rapid and high aeroplane or balloon ascents but in ordinary altitudes of mountains they are rare and some other cause should be looked for Those who remain at a high altitude or work constantly in a low oxygen partial pressure rapidly develop a polycythemia and increased hemoglobin with a low color index This is one of the most important factors in acclimatization All the usual symptoms can be accounted for by anoxemia If this is rapidly induced and is extreme unconsciousness and death may result

In the high altitudes of mountain climbing colossal feats of endurance have been accomplished as in the series of attempts to conquer Mount

Everest Mountain climbers must necessarily be in the best of physical condition and except for amateurs, or at great heights (26,000 feet), "mountain sickness" or "soroche" does not occur On the other hand, rapid ascents by railway as at Pikes Peak, in Peru and Chili, by aeroplane or by balloon, symptoms usually develop between 8,000 and 10,000 feet in those who are not acclimatized From this height upward the onset of symptoms varies with the individual It is, however, important, as flying is becoming increasingly popular, to appreciate that infrequent aeroplane flights of a few hours' duration do not conspire to produce acclimatization Even experienced pilots who fly constantly should not attempt an altitude of more than 12 000 feet without oxygen The onset of disabling symptoms is so insidious that unconsciousness may imperceptibly supervene But even more important than these extreme effects are the minor ones such as impaired coordination, ataxia, disturbed vision delayed reaction time, mental confusion and physical lethargy It is obvious since commercial flying is being conducted at higher altitudes, that every precaution should be taken to prevent these effects as they no doubt may contribute to accidents from errors in judgment and lack of control To a large extent these effects have been circumvented by construction which permits the barometric pressure within the aeroplane to be kept at a normal level or around 760 mm Hg Acute infections periods of convalescence, and fatigue all reduce one's capacity for acclimatization

This subject cannot be concluded without reference to a number of other important causes of anoxemia from lowered percentage of oxygen (IV above) These are principally encountered in mining as follows

1 **Black Damp or Choke Damp**—This is applied to an atmosphere in a mine where there are no symptoms of acute anoxemia, but where a candle will not burn, or when the oxygen in the inspired air is reduced to about 17 per cent Carbon dioxide may be somewhat increased, which is beneficial as it increases respiratory effort and in addition to extinction of the safety lamp, gives the miner warning of approaching danger

2 **Fire Damp** '—This is due to methane which is explosive in certain concentrations but for our present consideration it is important when it occurs in sufficient amounts to dilute the oxygen to a dangerous degree

3 ' **After Damp** ' indicates the presence of carbon monoxide This will be discussed in a separate section

4 **White Damp** —This is a mixture of carbon monoxide and steam in the air of a mine and is due to the heat produced by spontaneous oxidation of coal Its danger lies in the presence of carbon monoxide

The most common of the foregoing is black damp ' from the point of view of lowered O percentage This condition may be present in wells subterranean passages, long sealed cellars built in rock, abandoned mines and caves

Treatment—The treatment of mountain sickness" is rest and in emergencies, enriching the inspired air with oxygen But the latter does not help to acclimatization and if the patient is obviously seriously affected, return to a lower level is imperative Tachypnea with rales and other signs of pulmonary engorgement or edema also demand such a move There may be

pyrexia and tachycardia In situations where there is a low oxygen percentage its administration or prompt removal of the patient to ordinary air is indicated If respiration has ceased artificial respiration or the use of a respirator should be maintained for some hours before the case is abandoned as hopeless

MEDICAL PROBLEMS OF AVIATION

The medical problems of aviation are in great part due to rapid changes in man s physical environment to acceleration of movement in a centrifugal or centripetal direction, or to slower and more rhythmic deviations from a center of gravity Most of these problems are met with under other conditions or occupations but are acutely prominent in aviation through the rapid and extreme changes which are here encountered In order to avoid repetition but at the same time to focus attention on the newer aspects of these problems reference will be made to the sections where the fundamentals are considered while the specific implication will be dealt with here in more detail

Acute Oxygen Want

In the previous section and on page 179 under Cyanosis the effects of low partial pressure of oxygen in the alveolar air upon the oxygen saturation of hemoglobin have been dealt with As far as low barometric pressure was concerned this was only of medical importance in civilian life in mountain climbing and the occasional balloon ascents until the modern aeroplane was introduced A well trained individual can ascend with fair rapidity to between 8 000 and 12 000 feet above sea level without much disability But with the introduction of aeroplanes which ascend to an altitude of 40,000 feet or even higher at a speed of thousands of feet a minute new problems have arisen It is now a question not of what the machine can do but of what man can endure The highest altitude that man has survived in mountain climbing has been about 27 odd thousand feet (Mallory at Mount Everest) But this adventure was undertaken without oxygen being supplied In modern warfare the altitude to which an aviator may be forced is unpredictable Therefore, an oxygen supply for all personnel in the plane is obligatory and furthermore the mask and all its adjustments should be tested and found in proper working order before the flight is started

The symptomatology of acute oxygen want is most treacherous through the insidious character of its onset The first sensation may be a desire for somewhat deeper breathing This is most obvious when the victim is doing physical work otherwise it may pass unnoticed by the less observant At this time there may be a feeling of exhilaration which is most deceptive and often produces a false confidence which masks progressive incoordination and faulty judgment These features are soon followed by lethargy and rapid onset of unconsciousness During this period there is increasing cyanosis which in the earlier stages is frankly blue but gradually changes to a dirty greyish hue with profuse sweating which is quite similar to the facies of peripheral circulatory failure (see page 369)

It will be noted that the severe headache weakness and vomiting of mountain sickness are not prominent features This is quite explainable on the factor of time In rapid aeroplane ascents the anoxemia is produced very acutely

and the higher centers and vasomotor control are affected with explosive suddenness During prolonged flights at moderate altitudes (8,000 to 12,000 feet) these delayed symptoms and signs may be more prominent Furthermore acclimatization is not acquired in even relatively long aeroplane journeys nor do polycythemia changes in CO_2 combining power of the blood, and other biochemical changes develop

The only known sure means of preventing these results in aviation is by enriching the inspired air with oxygen or by increasing the barometric pressure within the aeroplane In rapid ascents this should be started before the plane leaves the runway and in slower ascents at 8,000 feet at the highest It is safer however, to have no exceptions The aviator in war is, as a rule, relatively youthful and youth is adventurous He does not tolerate additional encumbrances gladly and may consider himself above the laws of biophysics It is true that there is a zone of altitude (8 000 to 12 000 feet) in which men vary as to their susceptibility, but this is too narrow to be of much practical significance Therefore, rigid discipline in the use of oxygen should be enforced

Chronic Oxygen Want

It is a common observation that all people do not equally tolerate residence at high altitudes There are here excluded those who from some physical defect, apparent or masked suffer from insomnia extrasystoles respiratory oppression weakness or dizziness at such elevations as 1,000 feet The causes for these are not clear as the degree of oxyhemoglobin desaturation is negligible Rather we shall consider those who when first reaching 8 000 to 14 000 feet either have mountain sickness and soon recover or are very little troubled with symptoms In either case they may shortly acquire acclimatization not only as regards symptomatology but also biochemical and hematological factors In time, usually some months they develop irritability of temper, decreasing power of mental concentration easy fatigability menstrual irregularities lessened libido and a host of other minor complaints (see Neurocirculatory Asthenia page 373) It is presumed that these symptoms are due to chronic oxygen want This is probably so as no other common factor can be found

A similar train of symptoms may be found in aviators particularly those who frequently attain very high altitudes There is however an important difference The residents of high altitudes really do have a constant oxygen want while the aviator with a proper oxygen supply can ascend to 35 000 feet without any noticeable oxygen lack It may however be slight and oft repeated and with the addition of the stress and strain of flying over enemy territory open water anti aircraft barrages in intense cold with poor visibility and constant noise of considerable decibels a summation of factors is operative toward producing that elusive quality called chronic fatigue

Whatever be the cause it is a very real problem in aviation which comes entirely within the realm of the Medical Officer The only cure is a period of grounding with a change of environment conducive to physical and spiritual rehabilitation which is usually successful Salvage is important both for man power and machines

It is now well known that it cannot be produced experimentally in man in the quietness of a low pressure chamber with adequate oxygen supply even over periods of many hours a day for weeks

Low Barometric Pressure

The effects of rapid changes of barometric pressure apart from a strictly physical problem of solution of gases have been dealt with under caisson disease (see page 1457) In aviation the course of events is somewhat reversed In the former the victim proceeds from a higher positive pressure to a normal *pressure, while in the latter it is from a normal pressure to a rapidly diminish* ing one Speed is here the more important factor in precipitating these ill effects They are not as disabling as in "bends" but they are inconvenient in a number of ways The gastric and intestinal gases expand according to the usual laws of physics and lead to esophageal eructations, anal explosions a sense of abdominal tenseness and may even embarrass respiration through pressure on the diaphragm In more extreme cases there is a sensation of crackling in the hands and muscle cramps particularly on exercise The cerebral, spinal and myocardial effects are seldom seen Although at the present time it is a minor disability in aviators it must be given serious con sideration in anticipation of more rapid and higher altitudes and therefore certainty of closer approximation to caisson disease

Acceleration

The aviator particularly under combatant conditions must often change the direction of his flight with great suddenness This may produce, therefore, considerable centrifugal force upon the internal anatomical structures if the force of gravity is operating toward the periphery or away from the thorax and head if it be the opposite it is toward the thorax and head and away from the extremities This force is determined by a simple equation according to Newton s law $F = M A$ therefore $A = \frac{F}{M}$ when acceleration is proportionate to force and inversely proportionate to mass In curved flight the acceleration effect depends upon the rate of change of direction and the speed It can be expressed in the formula $F = \frac{M V^2}{r}$ (V = velocity M = mass and r the radius) It has become customary to express this unit as so many G's comparable with the number of times greater or less than gravity

It is not our purpose to enter into this further but to proceed to describe the effects of these variations in acceleration

Black Out

When an aviator comes out of a power dive or any similar maneuver which will effect a centrifugal force there are certain well known effects The force of gravity depending upon its intensity drives the blood to the periphery which will be to the abdomen legs and—to a less extent—the arms There is therefore an acute cerebral ischemia the diaphragm is forced downwards respiration is embarrassed and abdominal tension is increased The most im portant effect is a temporary but often disastrous loss of consciousness This

usually occurs at 5 + G's. The methods to overcome this have now been well worked out. They consist in principle in so encasing the operator at an automatic barometric normal environment through suitable clothing or in so conditioning the aeroplane that these changes in centrifugal force are not effective. For further discussion of these particular problems the reader is referred to standard texts and journals on "aviation medicine."

Red Out

When the acceleration is in the opposite direction the blood is driven toward the head and the diaphragm is fixed in extreme expiration. The latter is of little importance as the diaphragm is a powerful inspiratory organ. The effect on the circulation, however, is profound. Instead of the cerebral arteries and veins being almost empty and collapsed, they are full to the point of disaster. There is extreme headache of a bursting character, the vision becomes blurred as through a red mist (hence the name) and hemorrhages into the conjunctiva, retinae, inner ears, nasopharynx and, most important, into the contents of the closed cranium may result. Unconsciousness may occur also but it has a riotous onset compared to the smooth oblivion of the *black out*. The results of both may be the most bizarre neurological symptoms and signs.

This has been a most sketchy account of these conditions but it is as much as space will allow.

EFFECTS OF CARBON MONOXIDE

The effect of carbon monoxide could have been considered in the previous section without being out of place. We were dealing there with a reduced partial pressure of oxygen in the alveolar air leading to a deficient saturation of the hemoglobin and plasma with oxygen. In the present instance we will deal with a somewhat different process. The plasma of the arterial blood will contain a normal amount of dissolved oxygen but carbon monoxide has a greater affinity for hemoglobin than has oxygen. Therefore carbon monoxide hemoglobin will be formed and the combination of oxyhemoglobin prevented, in other words, the CO usurps the place of the O_2. In consequence the effects will be the same as if the partial pressure of oxygen were much reduced. The relative affinity of hemoglobin for these two gases is vastly different. It has an affinity for carbon monoxide 210 times greater than it has for oxygen. Therefore, a mixture of gases containing 0.07 per cent of carbon monoxide, 20.93 per cent of oxygen, 0.03 per cent of carbon dioxide, and 78.97 per cent of nitrogen would saturate the reduced hemoglobin equally as oxyhemoglobin and CO hemoglobin. From personal experience this produces moderate symptoms of anoxia after some time. The reason for the delay rests on the fact that the mixed venous blood contains only a relatively small amount of reduced hemoglobin and this will be saturated with CO but the oxyhemoglobin will remain undisturbed. As time passes the amount of CO hemoglobin will steadily mount until total equilibrium will be reached. There are several factors which hasten this. The most important is the amount of pulmonary ventilation, as when this increases the amount of CO supplied to the alveolar

air per minute increases Physical exercise not only increases this but also creates a greater demand for oxyhemoglobin which is continuously decreasing in amount as its place is taken by CO hemoglobin

Symptoms—The onset of symptoms in carbon monoxide poisoning is insidious, and the patient may be quite ignorant of his danger When the concentration in the atmosphere rapidly increases, unconsciousness may develop with alarming rapidity If it be less so headache and vertigo may be noticed with difficulty of vision and mental confusion The degree of saturation of the hemoglobin with CO at which these symptoms appear varies considerably in different individuals and there is no doubt that those who are frequently exposed to carbon monoxide may develop a considerable tolerance or accommodation to high percentages of CO hemoglobin This was particularly noticeable during World Wars I and II Men serving in "pill boxes" and in tanks were constantly exposed to a concentration which in time did not affect them but recruits frequently became unconscious In those unaccustomed to it symptoms (see above) usually appear when the saturation reaches about 25 per cent and are soon followed by coma The appearance of the patient is quite distinctive Although unconscious his color is good and the skin is warm but in the terminal stages respiratory failure supervenes and if there is sufficient reduced hemoglobin present in the capillaries cyanosis will appear while if there is vasomotor collapse the skin may be pale and clammy During the coma tetanic or epileptiform convulsions frequently occur and there is relaxation of the sphincters

Those who are constantly exposed to small amounts of the gas are supposed to develop a form of chronic poisoning characterized by headache, palpitation dizziness disturbance of gait tremors muscular twitchings and dyspepsia There may be either a polycythemia or a hyperchromic anemia

After a patient has been unconscious and has recovered from the effects of the gas there may be a residue of headache lassitude amnesia and various other nervous disturbances He usually completely recovers in twenty four to thirty six hours except in the severe cases in which coma has been prolonged when dementia may result as the damage to the higher centers has been irreparable Cerebral hemorrhage particularly in the basal ganglia has been reported with hemiplegia monoplegia paraesthesia and other prominent central nervous system disturbances There is no evidence that this is due to a directly toxic effect of carbon monoxide but rather to extreme anoxia Animals may be kept in a lethal concentration of CO but under a sufficiently high barometric pressure to charge the plasma with enough oxygen in solution to supply the tissues In spite of practically complete saturation of the hemoglobin with CO these anatomical lesions do not occur

Diagnosis—The diagnosis usually rests upon the coma and the history of exposure to carbon monoxide from some known cause such as illuminating gas automobile exhaust in closed garages in coal mines from charcoal braziers in unventilated rooms the imperfect explosion of munitions slowly burning fires in lime or brick kilns and from all smoldering fires in which there is incomplete combustion due to lack of oxygen

The *specific diagnosis* can be made by detecting carbon monoxide hemoglobin. Blood when drawn with oxalate has a carmine like appearance, which to the initiated is easily detected. It may be determined chemically by the pyrogallic tannic acid test. The most accurate method of estimating the amount present in the blood is by the photoelectric colorimeter devised by Evelyn. Spectroscopic methods may be employed, but these require expert knowledge, and with the usual instruments only large amounts can be detected with certainty.

Prognosis.—The majority of patients recover without any after effects but if the blood has been saturated to 75 per cent, and the patient has been unconscious for more than half an hour, death usually occurs.

Treatment.—The patient should be immediately removed from the environment of carbon monoxide and if the breathing has ceased, or is irregular with long periods of apnea, artificial respiration should be immediately instituted. Mechanical devices are to be condemned except the type of respirator devised by Drinker. These measures can be aided by the inhalation of 7 to 10 per cent carbon dioxide with oxygen until respirations are permanently established at a normal level. All patients do not respond equally well to the same concentrations of CO_2, some requiring higher percentages than others. It should be increased until deep respiratory movements are established. Intravenous injection of methylene blue has been advised in the treatment of this condition on the principle that it acts as a catalyst.

CYANIDES

The use of cyanides for suicidal purposes has had a vogue from time to time. It produces almost instantaneous death. However, since the introduction of these compounds as vermifuges in the fumigation of ships, dwellings, etc., infested with cockroaches, bedbugs and other parasites, it has become a more common danger due to the fact that a wider zone of environment may be polluted.

The action of the cyanides (hydrocyanic acid, cyanogen, etc.) is to inhibit cellular oxidation immediately. The fumes are inhaled even though there may be an attempt at swallowing some of these compounds.

The victim is unaware of the presence of the fumes even in high concentration and instantly loses consciousness and dies. In greater dilution there are dizziness, incoordination and rapid inability to perform muscular movements. As oxidation is arrested, or at least decreased, there is reduced consumption of oxygen and therefore no cyanosis even though respirations are arrested, but there is a peculiar and distinctive pinkish violet tint to the skin and mucous membranes due to the presence of cyanhemoglobin. The various cyanides should only be used in treatment of hypertension with a thorough understanding of their action and dangers.

Diagnosis.—The diagnosis rests upon the instantaneous action of the poison and the color of the skin, supported by the probable pollution of the atmosphere or the presence of a container from which the poison may have been taken, as the suicide has not time nor opportunity to dispose of it.

Prognosis—The prognosis is always extremely serious Death is often instantaneous In milder intoxications recovery may occur

Treatment—The treatment consists primarily in prevention by strict enforcement of the use of respirators by those entering places where cyanide fumigation has been done followed by thorough ventilation, particularly of pockets where free air currents do not have access The fumigation of apartments and rooms in dwellings must be conducted with scrupulous care that the fumes cannot penetrate to occupied rooms by means of flues dumb waiters, service elevators laundry and garbage chutes etc

There is little specific active treatment that can be used In borderline cases methylene blue has been advised on the principle of its acting as a catalyst Experimental evidence would indicate that it may be of benefit when a minimal sublethal amount of cyanide has been present in the atmosphere Its use has also been referred to in carbon monoxide poisoning

BENZENE POISONING

Benzene (Benzol C_6H_6) poisoning is due to the inhalation of benzene fumes *This substance is a colorless volatile liquid the vapor of which is* three times as heavy as air It is without odor and nonirritating It has been *used principally as a solvent* and was a favorite substance for cleaning clothes but has been largely discontinued because of its inflammability and toxic effects It is still employed however in the extraction of fats and oils and is a constituent of rubber cement but even for this last use it has been largely replaced by latex a liquid rubber In chemical industry it plays an important part in the production of aniline dyes phenol and picric acid and is also a constituent of many motor fuels It will be seen therefore that it still has a wide use

Its toxic effect *is in direct proportion to its* concentration in the atmosphere and the inhalation of fifteen parts in one thousand parts of air is rapidly fatal while the continued inhalation of one part in fifteen thousand will produce signs of chronic intoxication All people are not equally susceptible but young women are supposed to be particularly so

Symptoms—In acute poisoning occurring with high concentrations of the gas there is a rapid onset of dizziness mental confusion incoordination coma and death This may occur with great suddenness particularly in the benzene industry when men are exposed to a high concentration when cleaning or repairing machinery used in its manufacture or where it is employed as an adjunct in preparing other mixtures

In chronic benzene poisoning the progress of the disease is much more insidious The classical findings are described as a pan myelo toxicosis or aplastic anemia The erythrocytes may be reduced to under a million There is a leucopenia of less than one thousand resulting principally from a reduction of the granulocytes There is also a pronounced thrombocytopenia Therefore the symptoms are chiefly attributable to these severe blood changes and consist of weakness dyspnea palpitation dizziness and great fatigue Purpura and

hemorrhages from the mucous membranes are common, due to the thrombocytopenia There may be melena, hematemesis, epistaxis, hematuria, hemoptysis and bleeding from the gums Menorrhagia and metrorrhagia may be uncontrollable If the patient continues to be exposed irreparable damage to the bone marrow occurs More recent work has shown that this classical picture is only one of its manifestations It is now quite clear that in chronic poisoning the opposite of this description may be encountered there may be a polycythemia leucocytosis, leucemic or leucemoid blood picture, eosinophilia megalocytosis or microcytosis and immature marrow elements in the blood The bone marrow histology may range from severe hypoplasia to hyperplasia, and the latter may be so extreme as to simulate tumors In fact, acute myeloid leucemia and acute aleucemic leucemia have been reported Early anemia and macrocytosis are looked upon as the first signs in chronic intoxication, and it is now clear that men are just as susceptible as women and are at present more frequently exposed in industries Gant's test for decrease in the ratio of inorganic to organic sulphates is of great value but should be determined in the afternoon sample of urine

Diagnosis —The diagnosis of the condition depends upon the appreciation of the persistent exposure to the gas In the acute cases there is little doubt as to the diagnosis

Treatment —The treatment consists principally in prevention In industries where benzene is used, if there is a chance of its being present in high concentration proper respirators should be worn by the workmen Young girls should not be allowed to engage in any occupation where there might be exposure to benzene fumes In acute poisoning the victim should be removed to the open air and artificial respiration if necessary should be employed In the more chronic cases the victim should not continue to be exposed, and repeated blood transfusions are indicated to tide the patient over the period of severe anemia and thrombocytopenia, in the hope that the bone marrow function may be re established

OTHER GAS POISONS

The effects of the gases used in warfare have already been described In domestic life after carbon monoxide the most common causes of gas poisoning are from mechanical refrigeration These consist principally of methyl chloride which has a profound action upon the cerebral centers the blood and kidneys, and sulphur dioxide and ammonia which are violent respiratory irritants Nitric oxide was always a danger when inflammable x ray films were in common use It acts in a similar fashion to phosgene, having a direct action upon the alveolar epithelium and some hours after its inhalation acute suffocative pulmonary edema develops Its action is most insidious Hydrogen sulfide is a pronounced irritant to the eyes and may cause ulcerative keratitis It also, in concentrated amounts produces paralysis of the respiratory center and thus respiration may cease and the cardiac action continue It sometimes acts as a pulmonary irritant leading to pulmonary edema or bronchopneumonia

MOTION SICKNESS

Motion sickness is a clinical syndrome consisting of vertigo nausea and vomiting Some people develop these symptoms when subjected to unusual motions such as in a boat aeroplane, balloon railway train, or closed motor car It has been referred to in these special circumstances as "seasickness," "air sickness" or "car sickness" An individual who suffers from seasickness does not necessarily suffer from car sickness, and also there are individual variations as to the different ships A member of a crew may be quite free of all discomfort in a battleship but may be intensely seasick in a destroyer

Incidence—There are few records which afford definite knowledge as to the frequency of seasickness but such as are available would indicate that severe cases occur in about 0 5 per cent of the passengers carried, and to a less degree among the crew The relative immunity of the latter may be explained by the fact that adaptation often develops in those who take many sea voyages Animals, such as dogs horses, cows and sheep have been similarly affected, while hogs are thought to be immune It is less frequent in infancy and in old age It occurs in children but usually in a mild and transitory form

Etiology—The exact cause of motion sickness has been the subject of much speculation and has been attributed to many factors The balance of evidence would favor the conception that it is due to a disturbance, or increased sensibility of the labyrinthine apparatus as the symptoms can be closely simulated by syringing the ear with hot or cold water or by rotation (Barany test) and may also be produced in those susceptible by merry go rounds swings and elevators In the latter it is transitory Any motion which simulates these rotary movements such as the corkscrew movement rolling and pitching may produce these symptoms and signs The secondary or contributing factors are found principally in the central nervous system and the eyes are probably the most important particularly if the victim watches the horizon as it rises and falls Added to this is the disturbance of deep muscle sense and some have claimed that it most usually occurs in those with a vagotonic constitution Undoubtedly psychic factors are important and many people make up their minds that they are to be sick before the motion begins

The symptoms closely simulate those of mountain sickness and motion sickness can be aggravated by the habit of unconsciously holding the breath with the motion This is still further enhanced by watching the horizon

Symptoms—The symptoms in this syndrome vary considerably In the mildest cases there are a sense of tightness in the throat salivation with frequent swallowing and a "gone" sensation in the epigastrium Nausea and headache soon follow In appearance the victim is pale and there is a suggestion of cyanosis The symptoms may not proceed further than this and accommodation is soon established In more severe cases these symptoms are aggravated and the nausea culminates in explosive vomiting There are then vertigo incoordination and mental and physical lethargy Some victims are flushed while in others the pallor and cyanotic tint become more pronounced In the more severe forms prostration may become alarming There

are sweating, cyanosis, thirst, and collapse The skin is clammy, and the hands and feet are cold, the pulse is rapid and the body temperature is subnormal On account of the loss of gastric juice and the reduction in fluid intake the urine is scanty and highly colored, and may contain ketone bodies There is often pronounced dehydration with blood concentration The erythrocytes may number 8,000,000 to 9,000 000 per c mm Finally there is vasomotor collapse and the patient may appear in a dying condition

Diagnosis —The diagnosis is readily made Other conditions are seldom confused with it, although the contrary occasionally occurs when a too hasty diagnosis of motion sickness may overlook some more serious constitutional condition It assumed much prominence during the last war on account of its high incidence in the navy and air force and in the army in paratroopers and in amphibian operations

Prognosis —Recovery usually occurs in three or four days, but in some the symptoms continue in a modified degree for a long time when the abnormal motion persists Death does not occur from motion sickness but it may aggravate and render fatal other physical conditions Recovery is assisted by will power and living in the open air, as in time adaptation to the new environment is accomplished and this is definitely delayed by the individual's having a fatalistic attitude toward the sickness

Treatment —Prophylaxis would seem to be of considerable importance and this can be accomplished to some extent by careful attention to elimination If a voyage begins with a period of inland water travel or if during the first few days the sea is smooth and there is little perceptible motion to the ship passengers frequently acquire their sea legs so to speak and are then immune Those people who from experience are apprehensive of the condition during the first few days should spend as much time as possible in the open air and have their deck chairs placed in the middle of the ship They should wear dark glasses, and at all costs avoid watching the horizon or looking at the sparkle of the sun on the water The diet should be restricted to small amounts taken frequently and fluids should not be avoided but moderately restricted Once seasickness has become established there are many remedies with variable reputations Probably the best are those drugs which reduce the sensitivity of the labyrinthine apparatus and of these the bromides and barbiturates are the best Hypnotics should be used to give the victim a night s sleep as rest is imperative In severe cases with collapse the patient should be kept warm with blankets and hot water bottles The fluid intake should be maintained being given in small amounts and in the most severe cases it may be necessary to administer 5 per cent glucose saline solution intravenously Stimulants in the form of champagne whisky and brandy are favorite remedies If taken in sufficient quantities they would seem to produce a cure through their effect on the higher senses but most probably their chief effect is through suggestion Recent research has made strides in the prevention of this condition The drugs which have been found to be most effective are hyoscine belladonna and barbiturates in various combinations These are on the market under various trade names

SUBMERSION

This term is applied when an individual has been submerged in water for a short period and constitutes a form of suffocation which when death results is called drowning The victim may be unconscious and show all the evidences of imminent death The respirations may have ceased, or are in frequent and gasping The pulse is rapid and may not be palpated There are pallor and cyanosis, and the body surface is cold This form of suffocation differs from others in that although there may be a small amount of water in the lungs there is much more in the stomach Although the victim may ap pear dead when removed from the water energetic treatment should be im mediately instituted The clothing should be removed particularly over the upper part of the chest the patient should be laid out at length with the face downward but the head turned to one side and the tongue pulled forward *The rescuer should stand astride of the victim placing his hands under the* abdomen the patient is lifted in an attempt to empty as much liquid as pos sible from the stomach Artificial respiration by the Schaefer method should then be immediately commenced Rough handling should be avoided for fear of injury to the ribs and viscera Artificial respiration should be kept up for several hours, particularly if there is at any time a suggestion of a spon taneous respiratory movement If a respirator is available, the patient should *be placed therein The extremities should be massaged centrifugally only* Stimulants such as whisky strychnine caffeine camphor adrenalin etc are of little avail If a respirator is used or even with artificial respiration the inhalation of 5 per cent CO and 95 per cent oxygen is better than atmospheric air as it not only more readily overcomes the anoxemia but also acts as the best respiratory stimulant

EFFECTS OF RADIUM AND X RAY

It is not our purpose to deal with the local effects of irradiations whether from x ray or radium but rather to confine ourselves to a consideration of their more systemic reactions In those susceptible to these irradiations a syndrome may develop which is known as radiation sickness or radiation toxemia ' There develop shortly after exposure general malaise weakness headache and prostration There may also be nausea vomiting and diarrhea These symptoms can be prevented to a great extent or ameliorated by the use of nicotinic acid In addition to this immediate reaction anemia may develop in the course of several weeks if the exposures are continued The erythrocyte count may be as low as 2 500 000 and the hemoglobin 40 to 50 per cent More conspicuous is a leucopenia which occurs earlier and is more significant of del eterious systemic effects If the leucocyte count falls below 3 000 radiations should be immediately discontinued Although such blood changes develop with comparative rapidity in those who are particularly sensitive they may also occur in time in individuals who are not so afflicted but who are continuously exposed without protection to x ray or radium irradiations over a long period of time This was particularly common in the early stages of the use of the

x ray and radium. Since then accumulating knowledge has taught how to be protected from these effects. In certain instances a severe and fatal anemia has occurred.

A still more chronic effect is represented by the development of epitheliomata in the skin of the hands which are most exposed. In those working with radium who have survived the severe anemia, or in whom it did not occur, osteogenic sarcoma has been a late manifestation of the toxic effect of these emanations. In the cobalt mines of Schneeberg and the pitchblende mines of Joachimstal, in both of which the mine dust contains a considerable amount of radioactivity, bronchogenic carcinoma occurs in practically all miners who have been employed underground for more than a few years. More local effects occurred in radium dial painters who pointed their brushes by sucking them. This led to radium osteitis of the mandible or maxilla. In addition to this there also occurred the general symptoms of anemia of the regenerative, pseudoaplastic or pernicious type, and bone lesions. These were presumed to have resulted from the ingestion of minute quantities of radium over a period of time. Similar symptoms to those described above have developed in those employed in the refining of radium or mesothorium, in repairing radium needles, plaques and containers, and in the preparation of luminous paints. The recent vogue of drinking radioactive waters is not without its dangers. The natural or artificial waters which contain only gas emanations are probably harmless. On the contrary, waters made radioactive in various containers may possess quite dangerous qualities. This has been a fad of recent years which could in no way be beneficial except through suggestion.

There must also be mentioned the sterilizing effects on the gonads and ovaries. This at times is used for therapeutic purposes but may also result from indiscrete exposure of those who are employing these agents.

Radioactive substances, whether taken into the body by inhalation or ingestion, or directly through the skin, are absorbed and taken up in a colloidal form by the reticulo endothelial system (see page [illegible]76). Eventually they are removed from these cells and find their way to the bones, where they combine as carbonates and phosphates. The alpha rays comprise over 90 per cent of these radiations and therefore there is a constant bombardment of the internal environment by these rays which finally exert their greatest effect upon the bone marrow, where there is produced a hypoplastic condition, particularly of the erythrocytic tissue, and a great impairment in the production of granulocytes. This bone marrow is finally replaced by fibroblasts. In addition there is an osteitis which leads to decalcification, fibrosis, and softening, which accounts for the frequent occurrence in these victims of spontaneous fractures.

The development of the "atomic bomb" and the emphasis upon its terribly destructive power have created a near panic in the world. The principal injuries from its use are divisible into two groups. The first are due to the blast and are entirely traumatic after the same manner as explosive bombs. The second are similar to those occurring on exposure to radium and x ray. The systems chiefly affected are the hemopoietic, dermal, reproductive, osseous, etc. Loss of hair has also been reported which is similar to that which results

from direct application of other radiations Flash burns occur with considerable frequency due to the radiant heat Which of these two groups is the more important has yet to be assessed as has also the ultimate prognosis in the second group

Diagnosis—The diagnosis rests upon the history of exposure, and the detection of the presence in the body of radioactive substances either during life or at postmortem This may be accomplished in two ways, either by detecting radioactive deposits by a Geiger Muller counter or by collecting the expired air in special containers and having it examined by experts in radon analyses

Course and Prognosis—The course and prognosis of harmful effects of irradiations from either x ray radium or nuclear fission depend upon the amount absorbed over a period of time and as some appear to be more susceptible than others there may be considerable variation from case to case but any amount of radium over 2 micrograms is almost certain to produce grave bone lesions

Treatment—The treatment is principally prophylactic, there being no specific treatment after certain amounts of radioactive substances have been absorbed Attempts have been made to eliminate from the bones that which has been more recently deposited by using parathormone and a low calcium diet but this is of little avail in the majority of these patients, as they seek medical advice long after exposure The anemia is best treated by liver extract but the results are only temporary Surgical and dental procedures are often required to alleviate local bone lesions

EFFECT OF ELECTRIC SHOCK

Electric shock may be induced either by currents of high voltage or of comparatively low voltage as those used for domestic implements or from lightning

Low Voltage—The standard voltage in domestic electric appliances is usually 110 to 120 volts and is considered to be harmless But if contact is made when the hands or the body are wet or are immersed in water there may be a fatal result This not uncommonly occurs when an individual in a bathtub attempts to turn off an electric light or to move electric implements such as irons fans or heaters

High Voltage—When an individual comes in contact with electrical currents of high voltage such as stepping upon a broken high tension wire or grasping one in the hands or by leaning against one as sometimes occurs in those employed in line work for electrical companies there is instantaneous contraction of all the muscles If the hand has grasped the wire it cannot be released and the individual is said to be frozen to it as long as the current continues Severe burns are produced in this manner which may completely char even the bones (electrocution)

Effects of Lightning—The number of volts which are contained in a lightning bolt must be enormous probably numbering millions and thousands of amperes Death when it occurs is probably instantaneous although it is variously estimated that about one half recover

The principal *symptom* from electric shock is coma with cessation of respiration, although the heart continues to beat until it ceases from asphyxia. In the nonfatal cases there are collapse, tremors, convulsions and during recovery vomiting and photophobia. Local burns, ecchymoses, and abrasions are almost constantly found in people struck by lightning.

The principal causes of death are ventricular fibrillation and respiratory arrest. Others suggested have been prolonged muscular tetany causing asphyxia, the delayed effects of burns, and tissue coagulation from intense heat production. If the ventricular fibrillation is permanent, death is certain to occur. In most cases however, prolonged apnea is more prominent than cardiac arrest.

Treatment.—The individual must be released by *shutting off the current* as soon as possible, *not* by being pulled away, as this will probably add another victim. Artificial respiration should be immediately instituted. This must be maintained for many hours, and is best carried out by the rescue crews of public utility organizations. These men are skilled in the performance of the Schaefer method and have resuscitated victims up to nine hours after the shock has been induced. The use of carbon dioxide in these cases has been of little or no benefit nor have the so called cardiac and respiratory stimulants; in fact valuable time may be wasted in delaying the institution of artificial respiration while these are being procured, or by interrupting it to administer them.

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CHAPTER XXIII

DISEASES DUE TO CHEMICALS AND DRUGS

INTRODUCTION

To accomplish a complete review of the toxic effects of all chemicals and drugs would rightfully require a treatise on toxicology, which is quite out of place in this volume There are, however, a number of chemicals and drugs which on account of their common use either in therapeutics, or as contaminants of food and water or because they are used for pernicious purposes and produce a habit will be considered in this section As they affect the individual by direct ingestion or injection, and not through change of the external environment, they are not strictly comparable with those dealt with in the preceding chapter

ETHYL ALCOHOL

Alcohol has been used as a stimulant or a narcotic since the earliest historical records, and has been produced from many substances by fermentation Symptoms of its toxicity usually appear when the blood contains 0 1 per cent and if the concentration be increased to 0 5 per cent the result may be fatal There is however a great variation in the susceptibility of different people to its toxic action and this is usually decreased in direct proportion to the duration of the habit In many people its use results in a habit ' and in these definite withdrawal symptoms are apparent when its consumption is discontinued The amount of alcohol consumed over a period of time does not in all individuals produce the same symptoms or the same degree of intoxication Therefore the results of its ingestion are not necessarily always the same

Acute Alcoholism

A small amount of alcohol whether in the form of spirits, wines or brewed liquors produces exhilaration and a general feeling of well being It decreases the sense of fatigue and gives to the individual an increased jollity and the idea of enhanced capacity for accomplishment and coincident importance but with larger amounts, particularly if taken in a concentrated form this stage is rapidly passed and the individual enters a phase of mental confusion, loss of memory and change of personality some individuals becoming noisy and boisterous and others morose and sullen There is muscular incoordination In some individuals this affects all extremities but in others chiefly the legs, and they may appear apparently sober until they attempt to walk The skin is flushed and moist, while the pulse is full and accelerated respirations are slow and deep If sufficient alcohol has been taken these symptoms may progress to somnolence unconsciousness and coma The pupils are dilated and the body temperature lowered These are important contraindications to its use when an individual is exposed to intense cold This stage may be followed by vasomotor collapse and occasionally death

Such acute forms of alcohol poisoning are usually rapidly recovered from, but their recognition is important in the differentiation of uremia apoplexy, fracture of the skull and other causes of coma The detection of the odor of alcohol on the breath should not be taken as an absolute diagnostic sign to the exclusion of other possibilities as an individual may have taken some spirits before an attack of uremia or apoplexy and there would be only a coincident relationship On the other hand through incoordination the individual may have fallen and fractured the skull or have been assaulted in a brawl

Treatment—The treatment of these acute cases is directed toward the removal of the stomach contents Although vomiting is frequent this should be supplemented by gastric lavage or an injection of apomorphine After the stomach is empty food of a liquid high caloric character should be introduced and the patient left alone in warm surroundings until the effect of the intoxication disappears

Chronic Alcoholism

This takes on a variety of forms Its principal effect is upon the nervous system although it may have an aggravating effect upon lesions of the cardiovascular system and liver There is no absolute proof that it can of itself initiate anatomical changes in these latter organs The principal evidence of chronic alcoholism is a depreciation of the mentality and personality of the individual Association of ideas memory initiative reasoning and judgment are all impaired while their emotional responses are explosive All these symptoms may be evident during intermittent periods of subacute alcoholism but as the practice of imbibing becomes continuous so may these changes become permanent After the individual has been without alcohol for some hours, as for instance after a night's sleep there is an intense craving for it There are pains in the limbs unsteadiness and tremor sweating and general depression A fair estimate of the degree of chronic alcoholism may be obtained by ascertaining how much alcohol the individual requires in the morning (often before breakfast) to prepare him for the day's work

There are a number of phases of chronic alcoholism to which particular names have been given the principal ones are the following

Alcoholic Trance or Automatism

This occurs in highly neurotic or psychopathic people and has also been associated with epilepsy heat stroke and cerebral injuries In the majority of people in whom this occurs a small amount of alcohol only is necessary to induce it There is an entire lack of orientation and they enter into a condition of trance in which they may do sensible things, but on the other hand may commit crimes or behave in a most absurd manner being quite unconscious of their actions

Delirium Tremens

This is a state of acute delirium usually preceded by certain premonitory signs such as euphoria excitement and restlessness It is seldom seen in wine and beer drinkers, being most commonly found in those who are habitual

CHAPTER XXIII

DISEASES DUE TO CHEMICALS AND DRUGS

INTRODUCTION

To accomplish a complete review of the toxic effects of all chemicals and drugs would rightfully require a treatise on toxicology which is quite out of place in this volume There are, however a number of chemicals and drugs which on account of their common use either in therapeutics or as contaminants of food and water or because they are used for pernicious purposes and produce a habit will be considered in this section As they affect the individual by direct ingestion or injection, and not through change of the external environment, they are not strictly comparable with those dealt with in the preceding chapter

ETHYL ALCOHOL

Alcohol has been used as a stimulant or a narcotic since the earliest historical records and has been produced from many substances by fermentation Symptoms of its toxicity usually appear when the blood contains 0 1 per cent, and if the concentration be increased to 0 5 per cent the result may be fatal There is however a great variation in the susceptibility of different people to its toxic action and this is usually decreased in direct proportion to the duration of the habit In many people its use results in a ' habit and in these definite withdrawal symptoms are apparent when its consumption is discontinued The amount of alcohol consumed over a period of time does not in all individuals produce the same symptoms or the same degree of intoxication Therefore the results of its ingestion are not necessarily always the same

Acute Alcoholism

A small amount of alcohol whether in the form of spirits wines or brewed liquors produces exhilaration and a general feeling of well being It decreases the sense of fatigue and gives to the individual an increased jollity and the idea of enhanced capacity for accomplishment and coincident importance, but with larger amounts particularly if taken in a concentrated form this stage is rapidly passed and the individual enters a phase of mental confusion, loss of memory and change of personality some individuals becoming noisy and boisterous and others morose and sullen There is muscular incoordination In some individuals this affects all extremities but in others chiefly the legs and they may appear apparently sober until they attempt to walk The skin is flushed and moist while the pulse is full and accelerated, respirations are slow and deep If sufficient alcohol has been taken these symptoms may progress to somnolence unconsciousness and coma The pupils are dilated and the body temperature lowered These are important contraindications to its use when an individual is exposed to intense cold This stage may be followed by vasomotor collapse and occasionally death

pletely oriented as to his surroundings, but the hallucinations continue Recovery is usual but the more severe cases may progress into a chronic delirium or dementia, or what is known as "Korsakoff's syndrome or psychosis"

Treatment—The treatment is the same as for delirium tremens but as the condition lasts longer it is imperative to maintain the nutrition, and this is best accomplished through a high carbohydrate diet rich in vitamins

Wet Brain

In prolonged chronic alcoholism, usually with a record of a number of attacks of delirium tremens, or a recent severe trauma, the patients sink into a state of semicoma with muttering delirium They lie flat on their back staring at the ceiling, and hold their arms upward before them as though they were trying to grasp something just beyond their reach, and this position sometimes simulates catalepsy The arms however, are not immobile but are constantly in a state of tremor, and there is a continuous mumbling of incoherent words They remain completely indifferent to their surroundings or their physical state When given food they make no attempt at swallowing and are aroused with the greatest difficulty There are tachycardia and low pyrexia *This state may last for weeks and the patient may become dehydrated,* emaciated, and pass into a state of collapse If and when recovery occurs, the convalescence is prolonged extending into months and there may be a permanent residue of mental depreciation or dementia

Treatment—The treatment consists principally in nursing and the maintenance of nutrition This is difficult on account of the patient's inability or lack of attempts to swallow and aspiration of food frequently leads to pneumonia which is practically always fatal *It may be necessary to feed the* victim either by a nasal tube or stomach tube and large quantities of water should be given either by mouth or by rectum through a Murphy drip Intravenous injections of 50 per cent glucose or 25 per cent sucrose are of great assistance in reducing the cerebral and meningeal edema

Korsakoff's Syndrome or Psychosis

Korsakoff's syndrome or psychosis is a combination of a delirium and polyneuritis There are profound personality changes the individual often being either maniacal or melancholic The attention may be fixed for a few moments but quickly wanders There may be loss of memory with falsification and the mental attitude is childish or even idiotic

The *anatomical changes* in this condition have been identified as a peripheral neuritis and a degeneration of the cerebral cortical cells There has been some doubt expressed as to whether it is altogether due to alcoholism but rather that these lesions are a result of avitaminosis especially vitamin B complex There is probably a combination of these causes The neuritis may involve all four extremities and the cranial nerves and may affect both motor and sensory functions The pupils are frequently unequal or contracted and sometimes have the features of the Argyll Robertson pupil

users of whisky, gin, brandy, and other spirituous liquors It may develop during a period of intense and persistent alcoholism or be precipitated in more moderate imbibers who have suffered a severe shock, accident, or acute infection, such as sunstroke fractures, operations, traumatic injuries and infections such as influenza, pneumonia, or erysipelas

Symptoms—The symptoms are more violent during the night than during the day, the most prominent being hallucinations of sight These may be concerned with the ordinary articles or animals of a household, or the individual's daily round of duties On the other hand they may take the form of terrifying animals of bizarre and unreal shapes and colors The individual has little or no conception of his surroundings, and fails to recognize familiar objects or people The memory is completely lost Some remain subdued and terrified while others are violent and noisy and try to escape from their unreal environment There are incoordination of the arms and legs, and a constant trembling of the limbs body and tongue, which interfere not only with coordinated action but also with speech

The constitutional reactions are sometimes pronounced There may be pyrexia tachycardia low blood pressure sweating complete anorexia and sleeplessness The attack usually continues in proportion to its intensity for a week to ten days and terminates almost by crisis when the patient falls into a deep sleep and wakens after ten to twenty hours in complete ignorance of what has happened hallucinations have disappeared but the mental processes are sluggish and uncertain

Prognosis—The prognosis is usually good unless there is an intercurrent infection or the individual has been debilitated from lack of nourishment and neglect

Treatment—The treatment consists of careful watching and absolute rest in bed All means should be taken to prevent struggling and full doses of sedatives such as bromides chloral paraldehyde and barbiturates may be given External hydrotherapy for the pyrexia and nervous agitation should be employed while if the temperature is subnormal warm baths with friction are beneficial A concentrated caloric and liquid diet should be given with large amounts of vitamin B complex by mouth and parenterally when possible Any coincident lesion should be suitably treated

Acute Alcoholic Hallucinosis

Closely allied to delirium tremens there is a condition called *acute alcoholic hallucinosis*" which differs from it in that the hallucinations are more likely to be auditory than visual and it is more apt to occur in young persons It may also closely simulate acute paranoia or persecutory insanity Voices and commands or upbraidings and accusations are heard which drive the patient into a state of terror and they often attempt suicide to escape from them The hallucinations are often attributed to people in attendance or the family and the patient is suspicious that food or drugs are poisonous

Course—The course is longer than in delirium tremens the attacks may last up to six or eight weeks During this time the patient may be com

there may be complete loss of sight due to retrobulbar neuritis There may be some improvement in vision for a while, but eventually there is permanent blindness

Treatment —*The treatment is directed toward removal of the alcohol from* the stomach by gastric lavage and combating the acidosis by alkalies The latter does not influence the ultimate course of the disease, and only helps to correct this single condition

GINGER PARALYSIS

Associated with prohibition there appeared during 1930 a group of cases of flaccid paralysis of the arms and legs This was traced to drinking an adulterated fluid extract of Jamaica ginger The neuritis was at first considered to be due to alcohol but it was later shown by Smith and Elvove that it was caused by an adulterant in the ginger which was a phenol ester having the properties of triorthocresylphosphate

OPIUM

Opium has been used by the laity apart from its medicinal indications for centuries In India and China this is customary among the general population and although it is a habit forming drug it is on record that among Orientals who use it in moderation they may do so for many years without any important deleterious effects With such people it is treated as a social custom rather than a vicious one and is comparable to the moderate use of alcohol in the occidental countries It is true that these people have great difficulty in giving up its use but there is no indication that they are required to increase their daily allowance Although it may be stated that they develop a habit for its use this cannot be looked upon as a very vicious one

On the other hand the use of morphine and heroin (and codeine as a substitute in times when neither of these can be obtained) leads to a most pernicious and progressive habit The addiction to morphine is frequently initiated by prescribing it indiscreetly for severe painful conditions such as trigeminal and other severe neuralgias tabetic crises etc If either morphine or heroin is to be prescribed the patient should be ignorant of their character particularly in those who are neurotic or emotionally unbalanced as they soon find that it gives them relief from their physical and mental agitations and an opportunity to forget the unpleasant past The heroin habit on the other hand is more usually acquired from social contact It is started in ignorance particularly among the young and as will be seen, leads to both social and physical degradation Codeine is a much less active drug and is taken with greater difficulty as the amounts required to produce an effect by mouth are large It cannot be obtained usually in a form for hypodermic use and therefore it is injected intravenously It is seldom that a codeine habitue is so by desire but rather from necessity

Morphine may be taken by mouth but more usually hypodermically while heroin is taken by mouth or as a snuff like cocaine The most common method of using opium is by smoking it This is the favorite method of the Orientals

Course.—The course is prolonged and the *outlook doubtful for* complete recovery. Their emotional reactions remain unstable, and the slightest amount of alcohol produces an acute recurrence of symptoms.

Treatment.—The only treatment is rest, good nursing, generous diet, vitamin B complex intravenously or intramuscularly, and time.

Peripheral Neuritis

A *peripheral neuritis* may occur in chronic alcoholics, particularly women. It is characterized by a *gradual onset with pains in the limbs* and subjective changes of sensation, with progressive weakness to paralysis. It first affects the *extensors of the legs* and feet, and then later the arms and hands, leading to *wrist drop* and *foot drop*. There are exquisite tenderness over the muscles, *ataxia, and often swelling of the extremities. There is now a body of opinion* which attributes this neuritis in large part to vitamin B deficiency. This may be *absolute from dietary lack* or *relative through* the fact that in intoxications like alcohol there is required a much larger intake of the vitamin to be effective. Recovery is usually complete, but in severe avitaminosis may take many months to years. The *treatment* should be directed to prohibition of alcohol and concentrated vitamin B by mouth and parenterally. In the meantime muscle tone and nutrition must be maintained by physiotherapy.

Dipsomania

In some people, particularly those with a family history of alcoholism, there may be periodic bouts of intoxication. These individuals go through life in definite cycles of sobriety and drunkenness. For months they may not take any alcohol nor have a desire, but for some unknown reason an irresistible craving for it develops and then they go on a bout for an indefinite period, or this may be precipitated by a single drink. In time this craving subsides, often terminating in an attack of delirium tremens, and when recovered they loathe and detest both alcohol and themselves and enter a period of total abstinence. These bouts closely simulate the cycles of manic depressive insanity, the alcohol representing the period of depression.

METHYL ALCOHOL

Methyl alcohol differs from ethyl alcohol in that it is not completely oxidized in the body, but formic acid is formed which has a specific toxic effect. This intoxication may be brought about either from drinking methyl alcohol or ethyl alcohol adulterated with wood alcohol, or in some occupations the fumes may be inhaled in sufficient concentration as to produce an intoxication closely resembling that of ethyl alcohol poisoning, but the symptoms are more unpleasant and consist of nausea, vomiting, abdominal cramps, diarrhea, and dizziness. Formic acid produces an intense acidosis leading to hyperpnea and dyspnea, which brings about a low CO_2 content of the alveolar air and also a low CO_2 combining power. There are cyanosis and intense thirst. Difficulty of vision is at first attributed to the intoxication, but in a few hours

Opium and its derivatives do not produce any demonstrable anatomical effects except those which result from malnutrition, lack of sleep, and personal neglect It is true that habitues are often pale and there is constant sweating, the pulse and respirations are slow, the pupils are dilated except when under the action of the drug when they are contracted There are usually absence of deep reflexes, paresthesia and hyperesthesia of the feet which may prevent walking

The most pernicious habit is that due to heroin Morphine is next and finally opium This is due not only to the ease with which heroin can be taken but also to the action inherent in its intoxication The gravity of the situation is also enhanced by the fact that the habit assumed almost the proportions of an epidemic among the younger generation during the 1930's This however has now considerably subsided due to the difficulty of obtaining the drug through the incessant vigilance of narcotic control In some countries its use is now prohibited even for medicinal purposes

Course—The course of the habit is determined by a number of factors If there is not the desire on the part of the individual to be cured, all attempts to this end are of little avail Although this may be brought about through force it is usual when the victim has been released from constraint that he returns to the habit On the other hand if there is a sincere desire to be rid of this awful curse, a return is less likely This is particularly the case in morphine habitues who have acquired the habit through its continued administration to relieve pain when this has ceased a patient may often be permanently cured However through the period in which the drug has been taken there has been a depreciation of moral sense and will power which is not the best equipment to protect from temptation an individual who has once known relief of unpleasant conditions by its use It has been stated by those competent to judge, that a heroin addict is seldom permanently cured The majority of these habitues are perverts and take a devilish delight in contaminating others The mental depreciation is more pronounced than with morphine

The effect of these drugs upon the patient's general condition renders him more liable to intercurrent infections and in this way his longevity is affected

Treatment—The treatment of the addiction can be carried out satisfactorily only in an institution They should be isolated and placed in competent hands Before the withdrawal of the drug is begun their general nutrition should be satisfactory If there is emaciation a high caloric diet is given for some days and the patient assured periods of rest and sleep During this time the minimal amount of the drug necessary to relieve symptoms can be ascertained but it must be remembered that these addicts are habitual liars and may have secreted a supply in the most unlooked for places Even with the removal of all their clothing small vials of the drug may be secreted in the mouth the nose and even the rectum and vagina This is to be suspected in those who are being subjected to a cure by force

There have been a number of methods proposed for the withdrawal of the drug many of which were not without their dangers It is the generally

and at one time was much more common among Occidentals than at present as they are now more addicted to morphine and heroin

There are considerable differences of susceptibility between people Some beginners are affected by very small amounts, but all rapidly acquire a tolerance which requires increasing amounts to be taken to produce the desired effects There are a few individuals who can restrict their daily allowance without any uncomfortable symptoms

Symptoms — *Acute opium poisoning* is characterized by coma, sweating pinpoint pupils and slow respiratory rhythm which may be reduced to two to six per minute This is the picture of the full toxic effect of this drug, the outstanding feature being resistance of the respiratory center to normal stimulation Therefore, it is best treated by inhalations of 7 to 10 per cent carbon dioxide with pure oxygen It may be necessary to place the victim in a respirator, and while this is in operation to have him inhale this gas mixture The stomach should be washed out as morphine is secreted by the stomach, and large amounts of caffeine given as it is up to a point, a physiological antidote On the other hand the general depressive effect upon the central nervous system can be counteracted by the use of picrotoxin given in 5 to 10 mg doses every half hour until there are muscular twitchings or spontaneous response to painful stimuli This treatment should be maintained until there is some evidence of the toxic effects subsiding This may take many hours Cardiac arrest is the final indication of death

The symptoms arising from *continuous use of opium* or its derivatives are roughly divisible into two phases With the first few doses there is a pronounced and pleasant euphoria which removes the victim to a high state of pleasant exhilaration which is almost beatific It is to reacquire this that the drug is repeated and this would be particularly desirable when the individual is suffering intense pain The effect of a single dose usually lasts about three to six hours and with the return of the pain there is naturally an urgent desire for its repetition If relief of pain was not the original reason for its use it may be repeated merely to recapture the former exhilaration If this is continued at frequent intervals over a period the pleasurable sensations disappear and are replaced by what are known as withdrawal symptoms' which chiefly consist of mental depression physical lassitude nausea and dyspepsia There is in addition an intense desire for the drug which is out of proportion to the physical symptoms complained of Up to this time there may be no outward or manifest sign as in alcoholism that the person is a victim of this habit but in time definite changes in personality appear They become selfish inconsiderate indifferent to their responsibilities, slovenly in personal appearance behavior and dress irritable suspicious and prone to outbursts of anger They have insomnia or fitful sleep disturbed by dreams They lose their initiative and ambition and being conscious of this leads to self condemnation remorse and inferiority but at the same time they are resentful of criticism or advice The more pronounced cases have hallucinations of sight and hearing loss of memory anorexia pruritis, nausea and constipation

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accepted custom now to proceed with the withdrawal in an orderly fashion When the minimal amount has been ascertained, this is reduced by 1/10 per day, so that at the end of ten days the total withdrawal is accomplished During this period the patient exhibits the usual withdrawal symptoms There are first yawning, restlessness trembling, abdominal cramps diarrhea and pains in the joints and muscles The patients are frequently violent, even maniacal and may require physical restraint They may refuse food and liquids, and rapidly lose weight and become dehydrated with concentration of the blood This condition should be prevented at all costs Some advise the use of codeine as a substitute during this period increasing the amount from ½ grain (0 03 gram) every four hours on the first day up to 5 grains (0 3 gram) every four hours by the fifth day This is continued for the rest of the period and for five days after complete withdrawal The amount of codeine is then rapidly reduced until at the end of five days no drugs are being used It must not be forgotten however that codeine is used by habitues of both morphine and heroin to tide them over a period when these drugs are not available and with the increasing difficulty of obtaining heroin codeine habitues are becoming more numerous In most places they have no difficulty in obtaining the drug but it cannot be obtained readily in a form suitable for hypodermic use They however become very skillful in its intravenous administration and if necessary will go to all lengths to procure it

COCAINE

The use of cocaine was more popular some decades ago than it is at present Its principal effects are to relieve pain and give a sense of mental and physical exhilaration and increased power Immediately after taking the drug the conversation of the addicts is glib and inconsequential but as its effect wears off they become restless have insomnia pains in the limbs tremors and choreiform movements They become suspicious unreasonable and fearsome particularly on account of auditory visual and tactile hallucinations They complain of creeping sensations in the skin as if they were being eaten by insects They are irritable and quarrelsome and acquire slovenly habits a neglect of personal hygiene and an indifference to food This is followed by pallor emaciation and general muscular debility

In a certain number of cases where the habit has been present for a long period acute delirium or insanity may occur All the delusions and hallucinations are exaggerated and they may become extremely violent Upon withdrawal of the drug the hallucinations quickly disappear but the delusions remain The *course* of this acute insanity usually covers a few weeks but there is often permanent mental depreciation

Cocaine like morphine but unlike alcohol may not give rise to symptoms which can be recognized in the early stages of the habit but as it progresses the rapid changes from exhilaration to depression the changes in personality neglect of the person and clothing should always arouse suspicion but they are so secretive and such inveterate liars that it may be difficult to detect them in the act, particularly as they seek solitude to enjoy its effects The presence of false ideas of persecution is most significant

It is easier to cure a cocaine habitue than one addicted to morphine or heroin, but on the other hand it is more difficult for these victims to remain cured

Treatment—The treatment is similar to that outlined for morphine They are less liable in the early stages of withdrawal to acute maniacal outbursts *and when this does occur, it arouses suspicion that morphine or heroin has* been used with the cocaine

Cannabis Indica

Synonyms—Indian hemp, Hashish, Marijuana

Symptoms—This drug has been used almost exclusively in Africa and eastern countries as a stimulant and intoxicant for centuries In recent years it has *acquired a vogue in America until at present it is used extensively* The drug is contained in the dried flowering tops of the female plants of *Cannabis sativa*, an herb of the family Moraceae When grown in tropical and subtropical countries it produces a larger amount of resin The highly active plant grown in India differed only in this regard to other hemps, although at one time it was considered a different species hence the name *Cannabis indica* It can be grown with great ease in North America in fact may be classed as a weed

In eastern countries the resinous exudation is employed as a beverage a sweetmeat and is also smoked but in America it is used in the form of a cigarette (called 'reefers) and the fumes are inhaled

The *acute* symptoms are exhilaration laughter singing and the response to rhythm allows of a more rapid tempo and improvisation becomes easy even for the mediocre musician Time and space become diminutive and much can be accomplished in a seemingly short period It does not affect all in the same manner—some become thoughtful others hilarious and some destructive They feel they can accomplish almost impossible feats with ease and the moral sense is completely submerged Memory of actions done under its influence are obliterated

The chronic effects lead to a progressive depreciation of mentality tremors physical weakness anorexia pallor icterus and decrease of sensation and sexual power There is reduction of will power and concentration In the most extreme cases maniacal or melancholic symptoms appear and in some there is a condition allied to delirium tremens with hallucinations and destructiveness Coma lasting some hours is common in those who desire its full effect

Cannabis indica has been used for many years in therapeutics as a sedative and an analgesic but recently it has been supplanted by other drugs

The **outlook** for the addicts is serious It is not as yet certain that withdrawal symptoms are important but rather that depreciation of the higher centers is more or less permanent and the desire to be cured is wanting

The **treatment** is similar to that of other drug addictions such as heroin and cocaine except that withdrawal symptoms are not prominent On the other hand the moral comeback may require prolonged care and close control Fatalities from its use are rare although there may be pronounced respiratory and circulatory depression associated with unconsciousness Recovery from this may take twelve to thirty six hours

BARBITURATES

With the recent introduction of preparations containing barbituric acid and its allied compounds, there has been an increasing incidence of poisoning from these substances They have become a household remedy for all and sundry causes of restlessness insomnia, and other results of mental agitation There is no doubt that many cases of poisoning by these compounds are mild attempts at suicide or at least are prompted by the desire to forget mental perturbation

The principal preparations of this group that have recently been reported as causes of death are the following

Veronal	Somnifen
Medinal	Nembutal
Allonal	Amytal
Pernocton	Ceronal
Phenobarbital (luminal)	Phanadorm
Sevenal	Gardenal
Dial	Evipan

These are undoubtedly a greater menace to life than is usually appreciated by the laity

Symptoms—The symptoms are a deep narcosis with stertorous respirations at first which later become rapid and shallow when many fine rales are heard in the chest indicating a degree of pulmonary exudate or edema There are pyrexia, tachycardia cyanosis and a leucocytosis which would all indicate pulmonary congestion even to a bronchopneumonia The depth of the narcosis and the severity of the pulmonary manifestations are in direct proportion to the amount of the drug taken The sleep may last for many days and respiratory depression may become alarming The reflexes are all depressed or absent and there is often incontinence of urine and feces

In addition to the above there is a group of people with a peculiar susceptibility to some of these preparations which are compounded with amidopyrine such as allonal asciatin cibalgin comfral oftalidon somnasal veramon, and veropyron In these patients a profound leucopenia develops which leads to symptoms and signs identical with those described under granulocytopenia or agranulocytic angina

Skin rashes of an erythematous type are common even with small amounts There are other symptoms of milder toxicity than those described above These are headache vertigo ataxia ocular disturbances and indistinct vision In susceptible individuals all these symptoms and even delirium coma and vasomotor collapse may follow comparatively small amounts

Diagnosis—The diagnosis is suggested by the narcosis and the presence of evidence that the patient has had such drugs in his possession or has been in the habit of taking them for insomnia

Prognosis—The prognosis depends upon the amount of the drug taken There are cases on record which have recovered after being unconscious for eight days Respiratory failure and pulmonary infections are the usual causes of death

Treatment.—The treatment consists in maintaining respiration and the prevention of aspiration of foreign materials and secretions. Inhalation of a mixture of carbon dioxide and oxygen is indicated when there are tachypnea and cyanosis. If the respirations become irregular or there are periods of apnea, artificial respiration must be instituted, or better still the patient placed in a Drinker respirator if one is available. The usually accepted stimulants such as strychnine, digitalis, and camphor are of doubtful value. Coramine and lobeline have been more recently advocated. Analeptics such as benzedrine and picrotoxin should be given in full doses short of convulsions. They must be continued regularly until the patient shows returning consciousness or until a fatal issue has occurred. The patient should be placed in a semireclining position, and if there is any danger of aspiration through depression of the swallowing reflex, food should be given by nasal feeding or a stomach tube. Fluids are given by rectum with the Murphy drip method. Careful nursing is of the greatest importance.

LEAD

Lead has been used in industry and arts for centuries and for most of these it has been well known that there was some association between its use and the appearance of divergent groups of symptoms. But it remained for Tanquerel des Planches in 1831 to correlate them.

Incidence.—Whereas up to about 1920 lead poisoning was by far the greatest industrial intoxication, it has conspicuously decreased since by the institution of preventive measures. These are now controlled by legislation and improved working conditions and education have done a great deal also to reduce its incidence.

Etiology.—Lead may enter the body by ingestion, inhalation, through the mucous membranes or the skin through hair dyes, cosmetics, and abrasions upon which lead lotions have been applied. Lead enters the gastrointestinal tract through contaminated foods or liquids. Acidulated water in contact with lead pipes or worms may dissolve sufficient lead as carbonate to produce intoxication. Food contaminated by lead from unclean hands, chewing tobacco and snuff with lead wrappers, painted cots, toys, and other articles which children may gnaw or chew may all cause intoxication. Devonshire colic from contaminated cider and colica pectonum from lead being added to wine to prevent its souring were well known causes of epidemics many years ago. Lead salts taken for suicidal purposes or to promote abortion are other ways by which it is ingested. But the most dangerous portal of entry is through the respiratory tract. Whereas the greater part of the ingested lead can be handled by the liver, that inspired is rapidly distributed through the body and can thus exert a concentrated toxic effect. It is principally inspired as dust in the form of white or red lead or as fumes from burning wood impregnated with lead in poorly drawing stoves in unventilated rooms.

Hair dyes and cosmetics are relatively common but often neglected means by which lead gains entrance to the body. Other portals which are often over

looked are lead acetate douches, lead fomentations and lotions, and astringent mouthwashes. The latter are not necessarily swallowed to produce intoxication.

Symptoms.—The symptoms of lead poisoning may be fulminating or chronic, and in the latter group the association of cause and effect may be difficult to detect.

Acute lead poisoning differs in no essential way from the chronic, except for the violence and suddenness of the symptoms. These are principally nervous and hematological manifestations. There may be acute weakness and convulsions followed by coma commonly called "lead encephalopathy." In other cases an acute anemia occurs which may be so intensively destructive as to produce hemoglobinuria. In less acute cases gastrointestinal symptoms may be more prominent. They consist of nausea, vomiting, abdominal colic and constipation, simulating intestinal obstruction with which it may be confused and the patient may be operated upon. Diarrhea or rather tenesmus, may sometimes be present. The period of exposure is less important in the acute cases than is the amount absorbed or inhaled although in some who are relatively susceptible this may be comparatively small.

Chronic lead poisoning may present a variety of different symptom patterns which often overlap in varying degrees in different cases. For convenience of description they may be described under the following headings.

Gastrointestinal System.—*Lead Colic*.—One of the earliest symptoms of lead poisoning of which the patient complains is abdominal colic with associated constipation. The colic is usually felt about the umbilicus and the lower abdomen being therefore particularly referred to the areas of visceral pain resulting from small intestinal and colonic spasm. The writer was able many years ago to view these spasms during the course of an operation for presumed intestinal obstruction. The intermittent segmental contraction of the small bowel and the colon presented a very striking picture. The abdominal wall is usually retracted but not rigid which with the absence of leucocytosis but a relative lymphocytosis and no pyrexia helps to differentiate lead colic from acute peritoneal inflammation. The author however has seen cases of acute lead poisoning with a leucocytosis as high as 22 000 per cu mm.

In cases of suspected lead poisoning the so called "blue line" on the gums should be looked for. It appears as a serrated or dotted line on the gum margin and can be well seen by the aid of a hand glass. It is to be differentiated from staining of the teeth. It is due to deposits of lead sulphide about the minute blood vessels in the papillae of the gums and is most evident when pyorrhea is also present. It is almost pathognomonic of the presence of lead and may be noted when the amount absorbed has not been sufficient to produce toxic symptoms. It is simulated by a similar line caused by bismuth.

Hematological System.—There often appears before the onset of lead colic a progressive pallor which is contributed to by destruction of the erythrocytes. The pallor is not altogether due to the anemia. This anemia is associated with a compensatory stimulation of the bone marrow. In addition the red cells show a basophilic granulation or stippling. These cells are presumed to be degenerating young reticulocytes. Although they are present

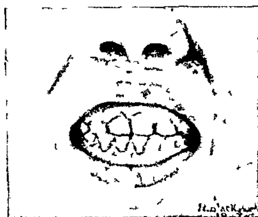


Fig [illegible] — A case of lead poisoning showing the blue line on the margin of the gums

in other conditions, such as pernicious anemia and leucemia, they are most abundant in lead poisoning, and when numerous are an important point in the diagnosis

Nervous System—It has already been mentioned how in acute lead poisoning convulsions and coma may develop and are known as "lead encephalopathy" This may also occur in the more chronic cases In addition many victims of lead poisoning may develop mental depression, occasionally delirium, and more rarely, acute mania with delusions In one group convulsions may be prominent, while in another the condition progresses to simulate general paresis

Lead palsy has been recognized for many years, and was graphically described by Benjamin Franklin early in the eighteenth century The first evidences of it are weakness and tremor The latter is quite characteristic and is best elicited by the outstretching of the hands The weakness becomes progressive until paralysis may develop As a rule it is painless The groups of muscles most used are those most affected, as in locomotor ataxia Therefore the right hand and arm are usually worse than the left developing finger and wrist drop as the extensors are more affected than the flexors In the leg peroneal paralysis is the most common There may also be optic neuritis It has recently been suggested that certain cases usually classified as disseminated sclerosis may be due to lead poisoning

Miscellaneous—For many generations gout has been associated with lead poisoning Reference has already been made to this (page 870) It has also been suggested, and clinical evidence presented that during attacks of acute lead poisoning there is a temporary hypertension The association of primary *contracted kidney and lead intoxication has been recognized for many years* Whether the ensuing degenerative renal changes are primarily caused by lead or are secondary to the arteriolar lesion is not as yet clear It is, however, one of the three principal conditions associated with this renal change (lead gout, essential hypertension)

Lead poisoning in children has recently been recognized as an important cause of disability *It has been stated above how they may ingest lead* through gnawing painted toys and furniture of the cheaper kinds The symptoms closely simulate those in adults, but there are certain ones which are more distinctive than others As children are subject to convulsions and gastrointestinal disturbances from many causes, they are not particularly indicative of lead poisoning On the other hand the outstanding sign is stippling of the erythrocytes The x ray pictures of the growing bones reveal white lines representing increased density These may be in series, progressing toward the metaphysis

Diagnosis—The diagnosis of lead poisoning rests principally upon the appreciation of the possibility that intoxication has occurred This is important when either the gastrointestinal neurological or hematological symptoms dominate the clinical picture The diagnosis of lead poisoning rests upon finding the 'blue line' in the gums and the presence of numerous basophilic granulations or stippled cells in blood smear Absolute con

firmation is obtained by detecting lead in the *feces or urine*. It is much more abundant in the former. During the *periods* when the greater part of the lead is found in the bones, little excretion may take place. In all *cases of* unexplained anemia or neurological lesions, lead poisoning should be suspected.

Prognosis.—The *course of lead* poisoning is usually chronic, although at any time acute *exacerbations with toxic* symptoms may occur which *give to the* disease a certain irregular periodicity. These periods are *coincident* with a low calcium diet or a mild acidosis. Lead is also released from the bones during *periods of intercurrent* infection which makes the diagnosis difficult as lead *intoxication* is masked by the presence of the more obvious condition.

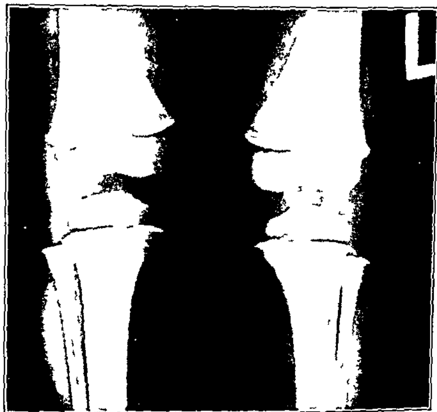


Fig. 14.—X-ray of the knee joint of a child suffering from lead poisoning. Note the lines of increased density at the ends of the bones.

Death may occur either from acute lead encephalopathy, diffuse peripheral neuritis (sometimes simulating Landry's *paralysis*), chronic debility with intercurrent infection or uremia in those chronic cases where cardiovascular renal lesions are prominent.

Treatment.—The prophylaxis of lead poisoning is of the first importance. In occupations where lead is used every precaution should be taken against its ingestion or inhalation. Lead should be prohibited in all apparatus used in distilling or condensing liquids for human consumption. Employees working in lead dust should be protected with respirators and lead must not be allowed to form part of cosmetics. Lead paint should not be permitted on toys, cots and

other indoor or outdoor furniture which may be accessible to infants The more unusual means whereby lead may enter the body are preventable chiefly through education

The active treatment of lead intoxication falls under two headings

1 Treatment of the immediate toxic symptoms
2 Removal of lead from the body or "deleading"

The toxic symptoms from lead are due to its circulation throughout the body If this can be prevented by elimination or by fixation in the bones, the symptoms will at least temporarily be relieved In the acute stages it is best to fix the lead in the bone It has been well demonstrated that any measure which increases the retention of calcium in the bones also binds lead Therefore a high calcium diet will operate to this end and the best means of accomplishing this is by giving a diet rich in calcium, containing such foods as egg yolk cheese milk, almonds beans oatmeal, turnips, carrots and oranges, and calcium lactate or gluconate in amounts of 2 to 4 grams daily This may be aided also by an alkaline diet or alkalies If there are acute cerebral symptoms or serious anemia calcium gluconate should be given intravenously 10 c c of a 10 per cent solution Calcium chloride must be avoided as it may produce an acidosis which releases lead from the stores in the bones

Urgent symptoms are usually rapidly controlled by these measures but if not sedatives may be required for the nervous symptoms, and morphia is particularly helpful for the intestinal colic

After having relieved the acute toxic symptoms the time has then arrived to proceed with removing the lead or "deleading" the patient This however must be undertaken with caution to avoid suddenly flooding the blood stream with lead and so reproduce the acute symptoms The process is the opposite to its fixation A low calcium diet consisting of bread potatoes rice tomatoes bananas apples corn meal tea coffee and some other vegetables and fruits will gradually release calcium and consequently lead from the bones This may be hastened by producing a mild acidosis preferably with ammonium chloride rather than the calcium salt But this must be used cautiously as it may likewise release the lead too rapidly Potassium iodide also increases the elimination of lead and similar caution must be observed Lead is secreted principally through the bowel and in less amounts in the urine

MERCURY

Mercury poisoning may be produced in a number of ways The more important are the ingestion of mercury bichloride with suicidal intent or accidentally during the mercurial treatment of syphilis and in industries particularly in quicksilver mines and in the beaver or velour hat trade When strong mercurial solutions were used for douches absorption by the vaginal and uterine mucosa was a common cause of intoxication

Mercury poisoning may vary in degree from an acute fulminating type to an extreme chronicity The severity of the symptoms depends entirely upon the amount of mercury absorbed in a unit of time and the susceptibility of the individual As much as 1½ grains (0 1 gram) has caused

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Mercury poisoning may vary in degree from an acute fulminating type to an extreme chronicity The severity of the symptoms depends entirely upon the amount of mercury absorbed in a unit of time and the susceptibility of the individual As much as 1½ grains (0 1 gram) has caused

death, while others have recovered from as much as 30 grains (2 gm.). If the mercury is ingested, the severity of toxic effects will depend upon the time which elapses between its ingestion and the induction of vomiting and the amount originally taken. On the average, 19 grains (1.25 gm.) with vomiting delayed for over half an hour results in death. The liver does not handle mercury to the same extent as it does lead and arsenic because it may appear in the urine within a few minutes after its ingestion, although the principal avenue for its excretion is through the colon.

Acute Mercury Poisoning

Acute mercury poisoning is usually produced by the ingestion of mercury bichloride and has been a favorite method of suicide.

Symptoms.—The symptoms may be divided into two stages. Immediately after the poison has been ingested there is a metallic taste in the mouth. Within a few minutes epigastric discomfort is felt, which shortly amounts to acute pain. Nausea soon supervenes and if there be immediate vomiting and the stomach is thoroughly emptied the chances of recovery are improved. In some, vomiting is delayed although there is intense nausea and retching.

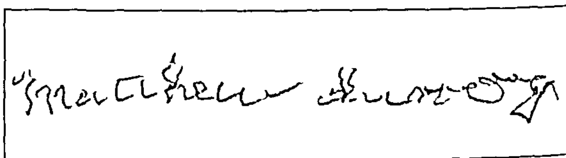


Fig. 1.—Handwriting of man with mercury shakes. (Courtesy of Dr. Francis T. Hunter.)

Retching is constant with eventually intense vomiting, and the vomitus may contain blood-stained mucus and desquamated mucosa. The severe abdominal cramps become general and are soon accompanied by diarrhea, tenesmus and bloody stools. There may also be collapse and death within twenty-four to forty-eight hours. In these cases the principal anatomical findings are an intense hemorrhagic gastroenteritis and colitis with early hepatitis. There is also a leucocytosis. All of these gastrointestinal symptoms may vary considerably according to the amount of poison taken and naturally the intestinal and colonic features will depend upon the amount which pass through the stomach.

The second important group of symptoms are those arising from the action of the mercury upon the kidney. There is an early oliguria. Such urine as is passed contains blood, albumin and many casts. There may be complete anuria. The interference with renal function is reflected in a steady increase of the nonprotein nitrogen, urea, creatinine and uric acid of the blood. There is also a progressive acidosis with declining carbon dioxide combining power. A moderate hypertension and slight general edema may fol-

low These cases either pass into a state of uremia, or if the damage is of a milder degree, renal function may be re established in a few days, and com plete recovery follow If the anuria persists longer than four days, a fatal result is to be expected

Anatomical changes in the kidneys are necrosis of the epithelium of the convoluted tubules, and to a lesser degree, of Henle's loops At the same time evidence of regeneration may be detected The patient may continue to ap pear in relatively good condition for many days and his appearance does not indicate the severity of the renal lesion

The causes of death in acute mercury poisoning are either collapse uremia, or infection from the acute gastroenterocolitis and stomatitis

Diagnosis —The diagnosis in these acute cases depends principally upon the history of the ingestion of mercury usually in the form of bichloride, or its detection in the vomitus or stools by the electrolytic method

Prognosis —The prognosis has already been indicated as depending upon the amount ingested and the time elapsing before the stomach is emptied either by vomiting or gastric lavage or both

Treatment —The treatment in the acute stages is principally the removal of mercury from the stomach If collapse occurs this is treated by the usual methods while the treatment of renal failure is the same as that indicated in acute nephritis This has now been improved by the use of the artificial kidney where by peritoneal lavage or by washing the venous blood through a dialyzable membrane the mercury and the noxious retention products may be eliminated and the nonprotein nitrogen may be brought to normal It re quires expert attention This principle rests upon the fact that acute mer cury poisoning causes a self limited lesion in the kidney which is reversible if life can be sufficiently prolonged

Chronic Mercury Poisoning

A subacute or chronic form of mercury poisoning may be found in those who are being treated for syphilis with mercury and in industries where mercury is *employed In the latter it is usually acquired through the respiratory tract as* the mercury is in a vaporous form as in quicksilver mines the manufacture of thermometers and barometers and all explosive fulminants of mercury

Symptoms and Signs —The symptoms and signs of the subacute form are those of an intense ptyalism There is first the characteristic metallic taste in the mouth soon followed by salivation and stomatitis The teeth are loosened and tender on pressure and the gums are swollen and have a bluish grey color as has also the mucous membrane of the tongue and mouth There is a distinctive fetor to the breath As the stomatitis progresses areas of necrosis appear on the tongue and mucous membrane of the cheeks and the cervical glands become enlarged The necrotic processes may extend to the bone principally the mandible

There is also a more *chronic form* in which the stomatitis is not so promi nent This occurs principally in those empoyed in quicksilver mines and in the hatters trade and more recently it has been reported in France in women

managing shooting galleries, the poisoning being derived from the fulminant mercury fumes from the exploding caps of the cartridges. A good description is found in the "Mad Hatter" in *Alice in Wonderland*, and in New England it is known as "Danbury Shakes." The outstanding feature is a fine but intermittent tremor in the hands. It is of the intentional variety and is aggravated by excitement and confusion, and these people often acquire a timid and sensitive nature. The tremor is well demonstrated in the character of their handwriting.

In 1942 Atkinson described a brownish colored reflex from the anterior capsule of the lens in those who worked for a long time with mercury or in an atmosphere containing mercury, although there were no symptoms of mercurialism (see Figs. 516 and 517). This is believed to be due to a deposit of mercury on or in the anterior capsule and appears to be permanent.

The *diagnosis* is not difficult, and the *prognosis* depends upon the duration of the illness. The *treatment* is confined entirely to removal from the environment of this chemical.

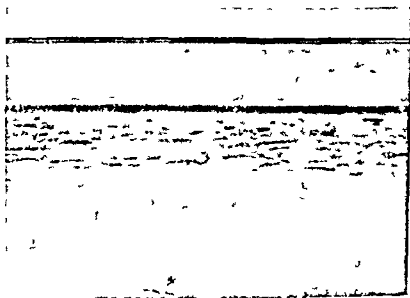


Fig. 518. Microphotograph of section of the lens showing deposit of mercury. (Courtesy of Walter S. Atkinson, Trans. American Ophthalmological Society, 1946.)

ARSENIC

Arsenic at one time was an important cause of epidemic intoxications, as for instance from the use of contaminated glucose or sulfuric acid in the manufacture of beer by the use of malt prepared with coke impregnated with arsenic, molds setting free fixed arsenic from wall papers, cosmetics containing arsenic, and in submarines through the arsenical fumes arising from the contents of the electric accumulators.

Acute arsenic poisoning due to suicidal or homicidal attempts falls into the realm of toxicology except so far as it arises from the therapeutic use of arsenic in the treatment of syphilis; this has already been dealt with (Chapter XIX).

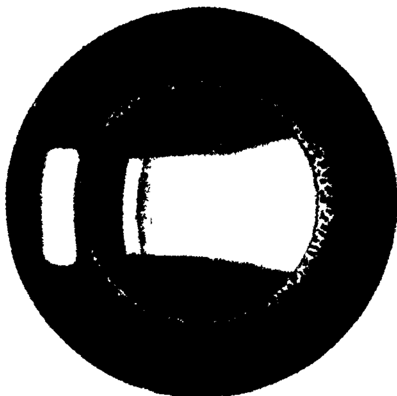


Fig 516 —Drawing of the slit lamp beam showing a rose-brown reflex from the lens (Courtesy of Walter S Atkinson Trans American Ophthalmological Society 194[illegible])

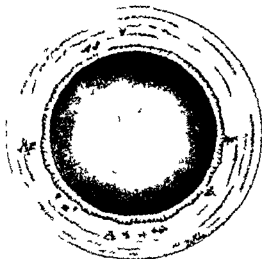


Fig 517 —Drawing to show the gray reflex of the lens on oblique illumination (Courtesy of Walter S Atkinson Trans American Ophthalmological Society 194[illegible])

Chronic arsenical poisoning may be found in those who are exposed to it in their occupation, and comes from the absorption of small amounts over a prolonged period. The onset is insidious, and the symptoms so indifferent as to be quite confusing. There are usually at first weakness with dyspepsia, anorexia, nausea and vomiting of mucus. If the atmosphere contains a toxic amount of arsenic, there may be nasopharyngeal catarrh, hoarseness, conjunctivitis, and in the more chronic cases indolent necrosis of the nasal cartilages. Skin eruptions are most important. There are usually erythema and swelling about the scrotum, perineum, axillae and groins where the skin is moist. Ulceration may occur. There is finally a generalized greyish pigmentation with gradually a patchy and coalescent hyperkeratosis chiefly on the palms and soles.

In addition to this sign there is often a low grade pyrexia and jaundice. The nervous system is particularly susceptible to its action; this leads to a form of peripheral neuritis chiefly indicated by sensory signs such as tingling, formication, burning, pain and anesthesia. Motor paralysis is rare. The cranial nerves are seldom affected although optic neuritis has been reported and mental deterioration occurs in the most chronic states.

Diagnosis.—The diagnosis usually rests upon the proof of exposure, but is suggested by the dermatological and neurological signs, and jaundice. The detection of arsenic in the stools or urine in abnormal amounts is conclusive.

Prognosis.—The prognosis depends upon the acuteness and severity of the intoxication. Those chronically exposed may develop a remarkable tolerance as among the "arsenic eaters" of Styria some of whom take 800 to 1 000 mg a week. There are persons who are quite sensitive; this is one of the dangers in the arsenical treatment of syphilis.

Treatment.—The treatment consists of stopping the intake and hastening elimination by free diuresis and catharsis. Calcium thiosulphate intravenously in amounts of 10 c c of a 5 per cent solution every other day, appears to help relieve the immediate symptoms. The specific antigas substance used against lewisite is also of great value in acute and chronic arsenical poisoning. It seems to be specially useful in exfoliative dermatitis.

PETROLEUM OR GASOLINE

The increasing use of internal combustion engines operated with gasoline or petroleum, and the constant use of these substances as household articles have produced a large number of poisonings from them. The fumes of gasoline present in the exhaust of these engines particularly if they are running in a confined and poorly ventilated space such as in tunnels or closed garages may produce an acute intoxication. It is difficult to be certain how much of this disability is due to the gasoline fumes, and how much to carbon monoxide. Experimentally pure gasoline fumes produce erythema, salivation, restlessness, muscular relaxation, coma, and sometimes convulsions.

Symptoms.—In man the specific symptoms are more commonly found when these chemicals are ingested either intentionally or by mistake. It is not unusual for children to swallow them. They do not produce any symptom in

the gastrointestinal tract, but when it volatilizes in the mouth and pharynx during the act of swallowing, the fumes are inhaled If in high concentration there is rapid unconsciousness, twitchings, convulsive seizures, and dilatation of the pupils These represent its anesthetic effect If the fumes have been still further concentrated signs of *asphyxia develop There is cyanosis, slowing respiration, and eventually respiratory failure* When they are absorbed from the gastrointestinal tract the fumes are eliminated through the lungs and through local irritation produce congestion edema and bronchopneumonia In these cases there is tachypnea pyrexia, and a taste of gasoline in the mouth for many days and even weeks

The **treatment** is purely symptomatic

ERGOT

Ergot poisoning is principally of a chronic type although acute cases are rarely encountered Chronic *ergot poisoning is mainly* caused by eating bread made from rye (black bread) the grain of which has been contaminated by a parasitic fungus *(Claviceps purpurea)*

Symptoms —The symptoms are of two types of poisoning the convulsive and the gangrenous

The **convulsive ergotism** is characterized by headache muscular cramps epileptiform convulsions and a small hypertensive pulse These may be preceded by vertigo and an itching crawling sensation in the skin In the severest cases somnolence stupor and coma may develop while in others there may be acute mania Associated with the muscular cramps there are tremors and contractures

Gangrenous ergotism presents a *picture somewhat similar to* that described under certain diffuse vascular diseases such as thromboangiitis obliterans Raynaud s disease and erythromelalgia and also may approximate in its early forms to the lesions of scleroderma and dermatomyositis There is apparently a progressive pressor effect upon the arterioles of the extremities and areas of pallor on the toes fingers nose ears and external genitalia are followed by gangrene of these parts An entire limb may be so affected Vesiculation with infection may lead to moist gangrene but in most cases it is of the dry type

Treatment —The treatment of course is principally prophylactic When the signs and symptoms first develop every precaution should be taken to prevent *further ingestion of this substance* The local vascular lesions are treated in the same manner as thromboangiitis obliterans and Raynaud s disease

FOOD

Many groups of symptoms are laid at the door of food poisoning and the diagnosis is used too loosely both by the laity and the profession There has been mentioned in the chapter on Diseases of Allergy that many individuals have a susceptibility to certain foods Although these could be termed "food poisoning" as far as the individual is concerned it cannot be so applied in the proper sense of the term, as it is the individual and not the food that is

at fault Many infections such as typhoid fever, bacillary dysentery, cholera undulant fever, and tuberculosis are acquired through the ingestion of food, water, and other materials contaminated by the specific organisms, and might with reason be considered as food poisonings " It is best, however, to confine this term to two distinct entities one of which is due to specific groups of organisms, and the other is caused by a specific toxin which is produced by an organism outside the body

FOOD INFECTION

The *salmonella group of bacteria occupies an intermediate* place bacteriologically between the coli and typhoid bacilli, and is sometimes called the intermediate group or the hog cholera, the enteritides, or the paratyphoid group Among these are found the specific organisms which produce food infection the principal ones being *Salmonella enteritides* (Gaertner bacillus), *Salmonella cholerae suis* (Hog cholera bacillus) and the *Salmonella aertrycke* All of them are gram negative nonspore bearing aerobic bacilli which do not ferment lactose

Another group of bacteria is the *Staphylococcus* of which the *aureus* is the most potent This is often the cause of severe local epidemics through the ingestion of infected foodstuffs chiefly custards pies ice cream etc

Symptoms —The incubation period is from four to twelve hours The onset as a rule is acute The first symptoms are nausea epigastric pain soon followed by vomiting and diarrhea The pain is of the colicky character and is sometimes most intense The stools are watery, have a foul odor, and their greenish color indicates the irritation of the small bowel There is pyrexia malaise weakness and prostration As a result of the vomiting and diarrhea *thirst and dehydration rapidly develop with oliguria*

The severity of these symptoms varies considerably not only in individuals but also in different epidemics In some they are fulminating and fatal within forty eight hours Their intensity is apparently due to the mass of infection and the virulence of the organisms

Diagnosis —The specific diagnosis of a salmonella or staphylococcus infection is often difficult There may be a history of having eaten tainted food often it is difficult to be certain of this It usually suggested itself to the mind of the patient by the development of the symptoms The cause may be suspected but a specific diagnosis can be arrived at only by the isolation of the organism from the suspected food or from the blood urine and feces of the patient This is seldom done except in well defined epidemics Agglutinins appear in the blood serum about a week after the onset of the disease and at this time the organisms have usually disappeared not only from the blood but also from the stools and the urine

Prognosis —The prognosis varies considerably from epidemic to epidemic The majority of cases recover with a prolonged convalescence The mortality is variously estimated as between 1 and 2 per cent

Treatment —The treatment is purely symptomatic Vomiting should not be prevented and gastric lavage should be supplemented to assist in removing from the stomach any remains of the infected material *High colonic irriga*

tions may give some relief to the intense diarrhea The acute abdominal pain and cramps may be alleviated by hot applications, and in many instances morphia may be required The dehydration resulting from the vomiting and diarrhea should be corrected by high fluid intake, and if necessary, intravenous saline glucose injections

FOOD INTOXICATION

(Botulism and Allantiasis)

In distinction to food infection food intoxication is the result of the ingestion of a virulent toxin produced by the *Clostridium botulinum* which is a spore bearing anaerobic bacillus It is a true intoxication the toxin being preformed before ingestion It occurs both in man and certain of the lower animals particularly chickens turkeys, ducks and water fowl (especially the wild duck) It is conveyed to man by contaminated preserved foods in which the bacillus has produced a varying amount of toxin At one time it was considered to arise only from potted meats but it has been clearly demonstrated that it may be present in preserved fruits and vegetables or in any food that contains protein The careful inspection of the manufacture of processed foods has led to a great reduction in the incidence of epidemics The majority of outbreaks are due now to foods preserved at home where they are not properly sterilized under pressure to destroy the spores of these bacteria

Symptoms—The incubation period is from twelve to twenty four hours but shorter periods have been reported probably due to the ingestion of a large quantity of toxin The onset is insidious but rapid The principal symptoms of botulism or food intoxication are weakness and paralysis The cranial nerves are conspicuously involved Gastrointestinal symptoms are not due to botulism but to some other concurrent infection There is a progressive involvement of the peripheral nerves Disturbances of vision appear early followed by blepharoptosis diplopia difficulty in talking swallowing and regurgitation of food through the nose due to paralysis of the palate when aspiration into the trachea may occur On examination the pupils are dilated there is absence of the light reflex and nystagmus The general muscular weakness is intense but there are no sensory disturbances and the disease is painless

The systemic symptoms are subnormal temperature, at first a bradycardia and then a tachycardia dyspnea and cyanosis due to respiratory paralysis which is the most common cause of death

Diagnosis—The diagnosis of this disease rests upon the characteristic symptomatology and the occurrence of the disease in a number of persons who have consumed the same food The absolute diagnosis rests solely upon the demonstration of the toxin by injection of tainted food into susceptible animals or the isolation of the organisms by suitable bacteriological methods There should be little difficulty in differentiating it from food infection On the other hand confusion may arise in distinguishing this condition from certain cases of encephalitis In botulism there is no change in the cerebrospinal fluid an important point in distinguishing it from cerebrospinal virus infections

Treatment —There is a specific botulism antitoxin, the efficacy of which depends principally upon its early administration Experimentally it is curative, but not after respiratory symptoms have developed In man its administration is frequently too long delayed It has been found experimentally that morphine delays the effect of the toxin As death is usually due to respiratory failure, and as the toxin is eventually destroyed or eliminated, it is important that artificial respiration be maintained either by the Schaefer method or better in a respirator, as long as life can be prolonged Some borderline cases are undoubtedly saved by this means

SNAKE BITES

From a practical point of view all snake bites should be considered as possibly poisonous Practically all snakes have a gland corresponding to the parotid of mammals which secretes a toxic substance These venom glands are connected with the hollow or grooved fangs of the snake and when a person is 'bitten'' by them (or stabbed by vipers) the venom is injected subcutaneously A goodly number of treatises have been published on snake bites and those who are particularly interested are referred to some of these

The venom toxins are in general twofold, the hematoxin and the neurotoxin The former produces hemolysis hemorrhagic extravasations, edema and local destruction of tissue while the latter specifically attacks the nerve centers and produces paralysis of the medullary functions Both these toxins are usually present in all venoms but in different proportions

Fresh venom when collected is colored a deep amber to a yellowish green and appears as a viscid fluid It is usually soluble after drying The venom of the viper is a good example of one that contains large amounts of the hematoxin The snakes of this type most frequently found in America are the rattlesnake, copperhead and the moccasin The cobras on the other hand, represent those whose venom is principally neurotoxic and in America the coral snake is the best representative of this species

Symptoms —The symptoms naturally vary with the predominating toxin injected Those produced by a hematoxic venom are usually a burning pain at the site of inoculation, a rapidly extending edema and dark discoloration of the skin due to extravasation of blood and destruction of the tissues There are nausea and vomiting vertigo rapidly followed by prostration cold, clammy sweat and coma The temperature is subnormal there is low blood pressure and death may occur in a comparatively short period During recovery jaundice is not unusual If a patient recovers from the acute hematoxic effects generalized edema may remain which when infected leads to extensive suppuration and gangrene

The inoculation of a venom containing principally neurotoxin produces much less local reaction and the signs of collapse are less severe The principal feature is dyspnea due to respiratory paralysis

There is little doubt about the *diagnosis*

Prognosis —The prognosis depends upon the type of snake bite and the duration before specific treatment is instituted the mortality varying with the different species from 10 to 35 per cent

tions may give some relief to the intense diarrhea The acute abdominal pain and cramps may be alleviated by hot applications and in many instances morphia may be required The dehydration resulting from the vomiting and diarrhea should be corrected by high fluid intake, and if necessary, intra venous saline glucose injections

FOOD INTOXICATION

(Botulism and Allantiasis)

In distinction to food infection food intoxication is the result of the in gestion of a virulent toxin produced by the *Clostridium botulinum* which is a spore bearing anaerobic bacillus. It is a true intoxication the toxin being pre formed before ingestion It occurs both in man and certain of the lower ani mals particularly chickens turkeys ducks and water fowl (especially the wild duck) It is conveyed to man by contaminated preserved foods in which the bacillus has produced a varying amount of toxin At one time it was con sidered to arise only from potted meats but it has been clearly demonstrated that it may be present in preserved fruits and vegetables or in any food that contains protein The careful inspection of the manufacture of processed foods has led to a great reduction in the incidence of epidemic The majority of outbreaks are due now to foods preserved at home where they are not prop erly sterilized under pressure to destroy the spores of the bacteria

Symptoms —The incubation period is from twelve to twenty four hours, but shorter periods have been reported probably due to the ingestion of a large quantity of toxin The onset is insidious but rapid The principal symptoms of botulism or food intoxication are weakness and paralysis The cranial nerves are conspicuously involved Gastrointestinal symptoms are not due to botulism but to some other concurrent infection There is a progressive involvement of the peripheral nerves Disturbances of vision appear early followed by blepharoptosis diplopia difficulty in talking, swallowing, and re gurgitation of food through the nose due to paralysis of the palate when aspiration into the trachea may occur On examination the pupils are dilated there is absence of the light reflex and nystagmus The general muscular weakness is intense but there are no sensory disturbances and the disease is painless

The systemic symptoms are subnormal temperature at first a bradycardia and then a tachycardia dyspnea and cyanosis due to respiratory paralysis which is the most common cause of death

Diagnosis —The diagnosis of this disease rests upon the characteristic symptomatology and the occurrence of the disease in a number of persons who have consumed the same food The absolute diagnosis rests solely upon the demonstration of the toxin by injection of tainted food into susceptible animals or the isolation of the organisms by suitable bacteriological methods There should be little difficulty in differentiating it from food infection On the other hand confusion may arise in distinguishing this condition from certain cases of encephalitis In botulism there is no change in the cerebro spinal fluid, an important point in distinguishing it from cerebrospinal virus infections

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Treatment — As soon as a victim is bitten by a snake a tourniquet should be applied a few inches above the point of inoculation. Incisions in a criss cross fashion through the skin with a knife or razor to open the fang punctures should be made. This will permit a forced suction by the mouth or by cups to promote a free flow of serum and lymph. If the edema should extend beyond the tourniquet an additional one should be applied and incisions and suction used through the edematous area.

The patient should receive as soon as possible an injection of antivenin. The amount given will depend upon the amount of toxin inoculated which will be in proportion to the size of the snake. It should also be in direct proportion to the interval between the inoculation and the application of antivenin. There are three principal antivenins prepared in America at the present time. One is more or less specific against the copperhead moccasin and rattlesnake while the other two are principally effective against the snakes of Central America. Unfortunately there are many varieties of rattlesnake, and therefore the antivenin is not as specific as could be desired. The injection should be repeated two or three times particularly in small people and children as the toxicity of the venom is in reverse ratio to the body weight.

The infiltration of the tissues about the site of the inoculation with 5 per cent carbolic acid has been advocated. The results are most encouraging and it has a further advantage that carbolic acid is readily available under most circumstances. Alcohol has been a traditional remedy. There is no evidence that it is specific but rather that it acts as a sedative and a reassurance to combat the terror expected by the victim. Pain is usually severe and should be relieved by analgesics or sedatives. In collapse intravenous saline solutions and at times blood transfusions are indicated.

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